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(54) **11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE S-OXIDE DERIVATIVES AND THEIR USE AS DOPAMINE D2 RECEPTOR ANTAGONISTS**

1-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPIN S-OXID DERIVATE UND IHRE VERWENDUNG ALS DOPAMIN D2 RECEPTOR ANTAGONISTEN

DÉRIVÉS DE 11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZÉPINE S-OXIDE ET LEUR UTILISATION EN TANT QU'ANTAGONISTES DU RÉCEPTEUR D2 DE LA DOPAMINE

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(56) References cited:
**WO-A1-2007/047737 WO-A1-2010/062565
WO-A2-2008/036139**

- **GERALD L. NEWTON ET AL: "Evaluation of NTF1836 as an inhibitor of the mycothiol biosynthetic enzyme MshC in growing and non-replicating Mycobacterium tuberculosis", BIOORGANIC & MEDICINAL CHEMISTRY, vol. 19, no. 13, 1 July 2011 (2011-07-01), pages 3956-3964, XP055140912, ISSN: 0968-0896, DOI: 10.1016/j.bmc.2011.05.028**
- **JINGBO XIAO ET AL: "Discovery, Optimization, and Characterization of Novel D 2 Dopamine Receptor Selective Antagonists", JOURNAL OF MEDICINAL CHEMISTRY, vol. 57, no. 8, 24 April 2014 (2014-04-24) , pages 3450-3463, XP055140768, ISSN: 0022-2623, DOI: 10.1021/jm500126s**

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Description

STATEMENT OF GOVERNMENT SUPPORT

[0001] This invention was made in part with government support from the US Department of Health and Human Services, National Institutes of Health. The government has certain rights in this invention.

BACKGROUND

[0002] G-protein coupled receptors (GPCRs) are among the most intensely investigated drug targets in the pharmaceutical industry. Over 40% of all FDA approved drugs target these important receptor proteins. Unfortunately, many of the ligands that are used as drugs or pharmacological tools are not selective and exhibit some unintended activity on non-target GPCRs or other proteins. This is because the orthosteric binding site is highly conserved among closely related types of GPCRs.

[0003] Dopamine receptors (DARs) belong to a large superfamily of neurotransmitter and hormone receptors. Five functionally active DARs have been identified in the mammalian genome. D_1-like DARs (D_1 and D_5) are Gas coupled, and D_2-like DARs (D_2, D_3 and D_4) are $G_{\alpha i/o}$ coupled. There are two isoforms of the D_2 DAR, short and long (D_{2S} and D_{2L}), respectively, which are derived from alternative RNA splicing and vary in the size of their third intracellular loops. The D_{2L} isoform is more prevalent, although both isoforms appear to be functionally similar. Amongst the DARs, the D_2 DAR is arguably one of the most validated drug targets in neurology and psychiatry. For instance, all receptor-based anti-Parkinsonian drugs work via stimulating the D_2 DAR (although controversy exists for a minor role of the D_1 DAR), whereas all FDA approved antipsychotic agents are antagonists of this receptor. The D_2 DAR is also therapeutically targeted in other disorders such as restless legs syndrome, tardive dyskinesia, Tourette's syndrome, psychosis, bipolar disorder, schizophrenia, and hyperprolactinemia. Most drugs targeting the D_2 DAR (orthosteric agonists and antagonists) are problematic, either by being less efficacious than desired or possessing limiting side effects, most of which are due to off-target cross-GPCR reactivity. It is thus desirable to develop a class of novel therapeutic agents with high selectivity for the D_2 DAR.

[0004] It should be noted that though the therapeutic potential for more selective D_2 DAR antagonists may be enormous, this approach may also provide a way forward for developing selective pharmacological probes. Amongst the D_2-like family of DARs (D_2, D_3, and D_4), only the D_4 DAR has ligands (both agonists and antagonists) that are truly specific, approaching 1,000 fold-selectively *versus* D_2 and D_3 DARs. This is not surprising given that the D_4 DAR is more structurally divergent compared to the D_2/D_3 DARs. D_2 and D_3 receptors share 78% homology in their transmembrane spanning domains, which harbor the ligand binding sites and thus the pharmacologic properties between these two receptor subtypes are quite similar. Therefore, it is very challenging to identify small molecules that can selectively bind to and/or functionally modulate either D_2 or D_3 DAR receptor subtypes. A high level of probe selectivity will allow for definitive *in vivo* studies of receptor function. With respect to the D_3 DAR, there are several compounds that exhibit good selectivity versus the D_4 DAR and moderate (a few hundred fold) selectivity versus the D_2 DAR. Some of these D_3-selective compounds have been used for *in vivo* experiments but the results have been controversial in many instances. In contrast, to the best of our knowledge, there are only few series of compounds that exhibit even moderate selectivity for the D_2 DAR receptor *versus* D_3 and D_4 within the D_2-like DAR subfamily. Selective antagonists of the D_2 DAR are useful for treatment of disorders currently treated with relatively non-selective D_2 antagonists, including Tourette's syndrome, tardive dyskinesia, Huntington's chorea, psychosis, bipolar disorder, depression, and schizophrenia.

[0005] Patients suffering from schizophrenia comprise the largest patient population that would benefit from highly selective D_2 DAR antagonists. Schizophrenia is characterized by delusions, hallucinations, social withdrawal, attention, and cognitive defects. All current FDA-approved antipsychotic drugs have D_2 DAR blocking properties. It is likely that D_2 DAR antagonism will remain a mainstay for the treatment of psychosis, especially for the treatment of so-called "positive" symptoms of this illness. Unfortunately, all antipsychotic drugs that antagonize D_2 DARs also interact with other GPCRs to varying degrees, including adrenergic, serotonergic, histaminergic, and cholinergic receptors. It is therefore not surprising that such drugs have multiple adverse effects including sedative, extra-pyramidal, endocrine, metabolic, and hypotensive properties. Because of the lack of highly selective ligands, it is not known to what extent other GPCRs contribute to the antipsychotic actions and/or associated side effects of these agents, although the H_1 histamine receptor has been implicated in weight gain.

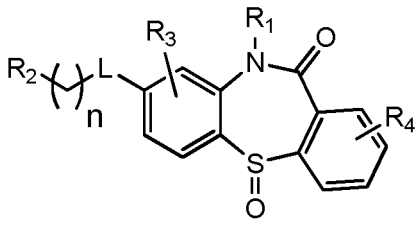
[0006] The present disclosure fulfills the need for highly selective D_2 DAR compounds and also provides additional advantages.

SUMMARY

[0007] The present disclosure provides and describes various dihydrobenzo[*b,f*][1,4]thiazepine-8-carboxamides with

selective affinity for the dopamine D_2 receptor.

[0008] In a first aspect the disclosure provides dihydrobenzo[*b,f*][1,4]thiazepine-8-carboxamide compounds of Formula I and the pharmaceutically acceptable salts thereof.



(Formula I)

[0009] Within Formula I the following conditions are met:

L is -NHC(O)-, -C(O)NH-, -OC(O)- or -C(O)O-;; and n is and integer from 1 to 4 and

is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0010] R_1 is hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, (C_3-C_7cycloalkyl)C_0-C_2alkyl, (mono- or di-C_1-C_4alkylamino)C_1-C_4alkyl, or (mono- or di-C_1-C_4alkylamino)C_1-C_4alkoxy.

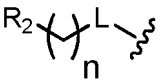
[0011] R_2 is a mono-, bi-, or tricyclic carbocyclic or heterocylic group, a (mono- or di-C_1-C_4alkylamino)C_2-C_4alkyl group, or C_4-C_8alkyl, each of which R_2 is unsubstituted or substituted with one more substituents independently chosen from halogen, hydroxyl, amino, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, $-OR_{11}$, $-(CH_2)_{0\text{-}4}C(O)R_{11}$, $-(CH_2)_{0\text{-}4}NR_{11}R_{12}$, $-(CH_2)_{0\text{-}4}C(O)NR_{11}R_{12}$, $-(C_{H2})_{0\text{-}4}N(R_{11})C(O)(R_{12})$, $-(CH_2)_{0\text{-}4}C(O)OR_{11}$, $-(CH_2)_{0\text{-}4}OC(O)R_{11}$, $-(CH_2)_{0\text{-}4}C(S)R_{11}$, $-(CH_2)_{0\text{-}4}S(O)_aR_{11}$, $-(CH_2)_{0\text{-}4}S(O)_bNR_{11}R_{12}$, $-(CH_2)_{0\text{-}4}N(R_{11})S(O)_bR_{12}$, where a is 0, 1, or 2, and b is 1 or 2.

[0012] R_{11}, R_{12}, and R_{13} are independently chosen at each occurrence from hydrogen and a C_1-C_6aliphatic group; each of R_{11}, R_{12}, and R_{13} is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, vinyl, allenyl, oxo, cyano, amino, -COOH, C_1-C_6alkyl, C_1-C_6alkoxy, (mono- and di-C_1-C_6alkylamino)C_0-C_2alkyl, C_1-C_6alkylester, C_1-C_6alkylthio, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0013] R_3 and R_4 are 0 or 1 or more substituents independently chosen from halogen, hydroxyl, amino, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, (mono- and di-C_1-C_4alkylamino)C_0-C_2alkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0014] Within Formula I, when R_1 is ethyl,

[0015] The group



[0016] is not 4-methoxybenzyl-NHC(O)-, pyridin-2-ylmethyl-NHC(O)-, 3-(morpholin-1-yl)propyl-NHC(O)-, 3-(azepan-1-yl)propyl-NHC(O)-, 3-(azepan-1-yl)ethyl-NHC(O)-, 3-(pyrrolidin-1-yl)propyl-NHC(O)-, 3-(4-methylpiperazin-1-yl)propyl-NHC(O)-, 3-(piperidin-1-yl)propyl-NHC(O)-, di-isopropylaminopropyl-NHC(O)-, di-propylaminopropyl-NHC(O)-, dibutylaminopropyl-NHC(O)-, or 3-(butyl(ethyl)amino)propyl-NHC(O)-. The disclosure also provides pharmaceutical compositions comprising a compound of Formula I together with a pharmaceutically acceptable carrier.

[0017] The disclosure further describes a method of treating a disorder in which selective antagonism of the dopamine D_2 receptor provides effective relief comprising administering a therapeutically effective amount of a compound or salt of Formula I. The invention therefore provides a compound or salt of Formula I, for use in a method of treating Tourette's syndrome, bipolar disorder, tardive dyskinesia, Huntington's chorea, psychosis, depression, hyperprolactinemia, or schizophrenia.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018]

FIGURE 1. (A) Graphical representation of the dose response curves of Compound 1 in D_2 Ca^{2+} assay (circles, AC_{50} = 0.281 μM), D_2 β-arrestin assay (triangles, AC_{50} = 2.89 μM), and D_3 β-arrestin assay (diamonds, AC_{50} = 5.76 μM). (B) Graphical representation of the dose response curves of **1** in binding assays for D_1 (squares), D_2 (circles, K_i = 0.08 μM), D_3 (solid triangles, K_i = 0.48 μM), D_4 (stars) and D_5 (inverted triangles).

FIGURE 2. (A) Graphical representation of the dose response curves of Compound 55 in D_2 Ca^{2+} assay (circles, AC_{50} = 0.070 μM), D_2 β-arrestin assay (triangles, AC_{50} = 0.725 μM), and D_3 β-arrestin assay (diamonds, AC_{50} = 12.9 μM). (B) Graphical representation of the dose response curves of Compound 55 in binding assays for D_1 (squares, K_i = 67.1 μM), D_2 (circles, K_i = 0.1 μM), D_3 (solid triangles, K_i = 2.9 μM), D_4 (stars, K_i = 8.48 μM) and D_5 (invented triangles).

DETAILED DESCRIPTION

TERMINOLOGY

[0019] Compounds of the present disclosure are generally described using standard nomenclature.

[0020] The terms "a" and "an" do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term "or" means "and/or." The open-ended transitional phrase "comprising" encompasses the intermediate transitional phrase "consisting essentially of" and the close-ended phrase "consisting of." Claims reciting one of these three transitional phrases, or with an alternate transitional phrase such as "containing" or "including" can be written with any other transitional phrase unless clearly precluded by the context or art. Recitation of ranges of values are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges are included within the range and independently combinable. All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as"), is intended merely to better illustrate the disclosure and does not pose a limitation on its scope unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention as used herein. Unless defined otherwise, technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this disclosure belongs.

[0021] "Formula I" includes compounds and salts of certain subformulae, described herein such as compounds of Formula II to IV.

[0022] In certain situations, the compounds of Formula I may contain one or more asymmetric elements such as stereogenic centers, stereogenic axes and the like, e.g. asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. Formula I includes all stereoisomeric forms, including racemates, optically enriched, and optically pure forms. In addition, compounds with carbon-carbon double bonds may occur in Z- and E-forms, with all isomeric forms of the compounds being included in the present disclosure. In these situations, the single enantiomers, i.e., optically active forms can be obtained by asymmetric synthesis, synthesis from optically pure precursors, or by resolution of the racemates. Resolution of the racemates can also be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column.

[0023] The disclosure of Formula I include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example, and without limitation, isotopes of hydrogen include tritium and deuterium and isotopes of carbon include ^{11}C, ^{13}C, and ^{14}C and isotopes of fluorine including ^{19}F.

[0024] Certain compounds are described herein using a general formula that includes variables, e.g. R_1-R_4, n, and L. Unless otherwise specified, each variable within such a formula is defined independently of other variables. Thus, if a group is said to be substituted, e.g. with 0-2 R*, then said group may be substituted with up to two R* groups and R* at each occurrence is selected independently from the definition of R*. When a group is substituted by an "oxo" substituent a carbonyl bond replaces two hydrogen atoms on a carbon. An "oxo" substituent on an aromatic group or heteroaromatic group destroys the aromatic character of that group, e.g. a pyridyl substituted with oxo is a pyridone.

[0025] Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. A stable compound or stable structure is meant to imply a compound that is sufficiently robust to survive isolation from a reaction mixture, and subsequent formulation into an effective therapeutic agent.

[0026] The term "substituted" means that any one or more hydrogen atoms bound to the designated atom or group is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded. Unless otherwise specified substituents are named into the core structure. For example, it is to be understood that when (cycloalkyl)alkyl is listed as a possible substituent the point of attachment of this substituent to the core structure is in the alkyl portion.

[0027] Substituents are named into the ring unless otherwise indicated. A dash ("-") or a double bond ("=") that is not between two letters or symbols indicates the point of attachment for a substituent. For example, $-CONH_2$ is attached through the carbon atom.

[0028] An "aliphatic group" is a non-aromatic hydrocarbon group having the indicated number of carbon atoms. Aliphatic groups may be saturated, unsaturated, or cyclic.

[0029] "Alkyl" includes both branched and straight-chain saturated aliphatic hydrocarbon groups, having the specified number of carbon atoms. Thus, the term C_1-C_6alkyl includes alkyl groups having from 1 to about 6 carbon atoms. When C_0-C_n alkyl is used herein in conjunction with another group, for example, (cycloalkyl)C_0-C_2 alkyl, the indicated group, in this case cycloalkyl, is either directly bound by a single covalent bond (C_0), or attached by an alkyl chain having the specified number of carbon atoms, in this case from 1 to about 2 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, and sec-pentyl. C_1-C_6alkyl includes alkyl groups have 1, 2, 3, 4, 5, or 6 carbon atoms.

[0030] "Alkoxy" is an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, 2-butoxy, t-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, n-hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

[0031] "Alkylthio" indicates an alkyl group as defined above attached through a sulfur linkage, i.e. a group of the formula alkyl-S-. Examples include ethylthio and pentylthio.

[0032] "Alkanoyl" is an alkyl group as defined above with the indicated number of carbon atoms covalently bound to the group is substitutes through a carbonyl (C=O) bridge. The carbonyl carbon is included in the number of carbons, that is C_2alkanoyl is a CH_3(C=O)-group.

[0033] "Alkylester" is an alkyl group as defined herein covalently bound to the group it substitutes by an ester linkage. The ester linkage may be in either orientation, e.g., a group of the formula -O(C=O)alkyl or a group of the formula -(C=O)Oalkyl.

[0034] "Mono- and/ or di-alkylamino" indicates secondary or tertiary alkyl amino groups, wherein the alkyl groups are as defined above and have the indicated number of carbon atoms. The point of attachment of the alkylamino group is on the nitrogen. Examples of mono- and di-alkylamino groups include ethylamino, dimethylamino, and methyl-propylamino. A "(mono- and/or di-alkylamino)C_0-C_2alkyl group is a mono and/or dialkylamino group as defined that is directly bound to the group it substitutes (C_0alkyl) or attached to the group it substitutes via a 1 to 2 carbon alkyl group linker.

[0035] A "carbocyclic group" is a monocyclic or bicyclic saturated, partially unsaturated, or aromatic ring system in which all ring atoms are carbon. Usually each ring of the carbocyclic group contains from 4-6 ring atoms and a bicyclic carbocyclic group contains from 7 to 10 ring atoms but some other number of ring atoms may be specified. Unless otherwise indicated, the carbocyclic group may be attached to the group it substitutes at any carbon atom that results in a stable structure. When indicated the carbocyclic rings described herein may be substituted at any carbon atom if the resulting compound is stable.

[0036] "Cycloalkyl" is a saturated hydrocarbon ring groups, having the specified number of carbon atoms, usually from 3 to 7 carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl as well as bridged or caged saturated ring groups such as norborane or adamantane. In the term "(cycloalkyl)alkyl," cycloalkyl and alkyl are as defined above, and the point of attachment in on the alkyl group.

[0037] "Haloalkyl" indicates both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen atoms, generally up to the maximum allowable number of halogen atoms. Examples of haloalkyl include, but are not limited to, trifluoromethyl, difluoromethyl, 2-fluoroethyl, and penta-fluoroethyl.

[0038] "Haloalkoxy" indicates a haloalkyl group as defined above attached through an oxygen bridge.

[0039] "Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, or iodo.

[0040] "Pharmaceutical compositions" are compositions comprising at least one active agent, such as a compound or salt of Formula I and at least one other excipient. "Carriers" are any inactive materials, including excipients and diluents, which may be added to the pharmaceutical compositions including carriers and diluents. Pharmaceutical compositions meet the U.S. FDA's GMP (good manufacturing practice) standards for human or non-human drugs.

[0041] The term "heterocyclic group" indicates a monocyclic saturated, partially unsaturated, or aromatic ring containing from 1 to about 4 heteroatoms chosen from N, O, and S, with remaining ring atoms being carbon, or a bicyclic saturated, partially unsaturated, or aromatic heterocylic ring system containing at least 1 heteroatom in the two ring system chosen from N, O, and S and containing up to about 4 heteroatoms independently chosen from N, O, and S in each ring of the two ring system. Usually each ring of the heterocyclic group contains from 4-6 ring atoms but some other number of ring atoms may be specified. Unless otherwise indicated, the heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. When indicated the heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. It is preferred that the total number of heteroatoms in a heterocyclic groups is not more than 4 and that the total number of S and O atoms in a

heterocyclic group is not more than 2, more preferably not more than 1. Examples of heterocyclic groups include, pyridyl, indolyl, pyrimidinyl, pyridizinyl, pyrazinyl, imidazolyl, oxazolyl, furanyl, thiophenyl, thiazolyl, triazolyl, tetrazolyl, isoxazolyl, quinolinyl, pyrrolyl, pyrazolyl, benz[b]thiophenyl, isoquinolinyl, quinazolinyl, quinoxalinyl, thienyl, isoindolyl, dihydroisoindolyl, 5,6,7,8-tetrahydroisoquinoline, pyridinyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, morpholinyl, piperazinyl, piperidinyl, and pyrrolidinyl.

[0042] Additional examples heterocyclic groups include, but are not limited to, phthalazinyl, oxazolyl, indolizinyl, indazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, benzoisoxolyl, dihydro-benzodioxinyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxazolopyridinyl, imidazopyridinyl, isothiazolyl, naphthyridinyl, cinnolinyl, carbazolyl, beta-carbolinyl, isochromanyl, chromanonyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl, 5 pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl, benzothiopyranyl, coumarinyl, isocoumarinyl, chromanyl, tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocoumarinyl, dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl, benzoxazolinonyl, pyrrolyl N-oxide, pyrimidinyl N-oxide, pyridazinyl N-oxide, pyrazinyl N-oxide, quinolinyl N-oxide, indolyl N-oxide, indolinyl N oxide, isoquinolyl N-oxide, quinazolinyl N-oxide, quinoxalinyl N-oxide, phthalazinyl N-oxide, imidazolyl N-oxide, isoxazolyl N-oxide, oxazolyl N-oxide, thiazolyl N-oxide, indolizinyl N oxide, indazolyl N-oxide, benzothiazolyl N-oxide, benzimidazolyl N-oxide, pyrrolyl N-oxide, oxadiazolyl N-oxide, thiadiazolyl N-oxide, tetrazolyl N- oxide, benzothiopyranyl S-oxide, and benzothiopyranyl S,S-dioxide.

[0043] "Heteroaryl" is a stable monocyclic aromatic ring having the indicated number of ring atoms which contains from 1 to 3, or in some embodiments from 1 to 2, heteroatoms chosen from N, O, and S, with remaining ring atoms being carbon, or a stable bicyclic or tricyclic system containing at least one 5- to 7-membered aromatic ring which contains from 1 to 3, or in some embodiments from 1 to 2, heteroatoms chosen from N, O, and S, with remaining ring atoms being carbon. Monocyclic heteroaryl groups typically have from 5 to 7 ring atoms. In some embodiments bicyclic heteroaryl groups are 9- to 10-membered heteroaryl groups, that is, groups containing 9 or 10 ring atoms in which one 5- to 7-member aromatic ring is fused to a second aromatic or non-aromatic ring. When the total number of S and O atoms in the heteroaryl group exceeds 1, these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heteroaryl group is not more than 2. It is particularly preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1. Examples of heteroaryl groups include, but are not limited to, oxazolyl, pyranyl, pyrazinyl, pyrazolopyrimidinyl, pyrazolyl, pyridizinyl, pyridyl, pyrimidinyl, pyrrolyl, quinolinyl, tetrazolyl, thiazolyl, thienylpyrazolyl, thiophenyl, triazolyl, benzo[*d*]oxazolyl, benzofuranyl, benzothiazolyl, benzothiophenyl, benzoxadiazolyl, dihydrobenzodioxynyl, furanyl, imidazolyl, indolyl, and isoxazolyl.

[0044] "Heterocycloalkyl" is a saturated ring group, having 1, 2, 3, or 4 heteroatoms independently chosen from N, S, and O, with remaining ring atoms being carbon. Monocyclic heterocycloalkyl groups typically have from 3 to about 8 ring atoms or from 4 to 6 ring atoms. Examples of heterocycloalkyl groups include morpholinyl, piperazinyl, piperidinyl, and pyrrolinyl.

[0045] "Pharmaceutically acceptable salts" includes derivatives of the disclosed compounds wherein the parent compound is modified by making non-toxic acid or base salts thereof, and further refers to pharmaceutically acceptable hydrates solvates of such compounds and such salts. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts and the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, conventional non-toxic acid salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxylmaleic, phenylacetic, glutamic, benzoic, salicylic, mesylic, esylic, besylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, $HOOC-(CH_2)_n-COOH$ where n is 0-4, and the like. Lists of additional suitable salts may be found, e.g., in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., p. 1418 (1985).

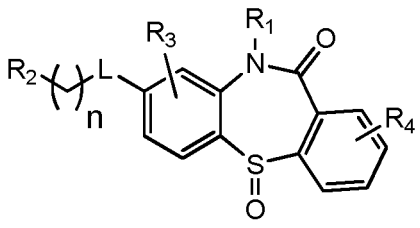
[0046] The term "carrier" applied to pharmaceutical compositions/ combinations of the invention refers to a diluent, excipient, or vehicle with which an active compound is provided.

[0047] The term "therapeutically effective amount" of a compound of Formula I, or a related formula, means an amount effective, when administered to a human or non-human patient, to provide a therapeutic benefit such as an amelioration of symptoms, e.g., an amount effective to decrease the symptoms of a central nervous system disorder, and including an amount sufficient to reduce the symptoms of a schizophrenia; Parkinson's disease (PD); dyskinesia; restless legs syndrome; depression; or the cravings associated with substance abuse. Thus a therapeutically effective amount of a compound is also an amount sufficient significantly reduce the indicia of the disease or condition being treated. The invention also includes, in certain embodiments, using compounds of Formula I in prophylactic treatment and therapeutic

treatment. In the context of prophylactic or preventative treatment a "therapeutically effective amount" is an amount sufficient to significantly decrease the treated patient's risk of exhibiting symptoms of the condition treated. A significant reduction is any detectable negative change that is statistically significant in a standard parametric test of statistical significance, such as Student's t-test, in which $p < 0.05$.

CHEMICAL DESCRIPTION

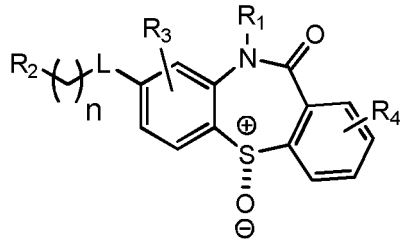
[0048] In addition to compounds and salts of Formula I disclosed in the SUMMARY section, the disclosure includes compounds and salts of Formula I



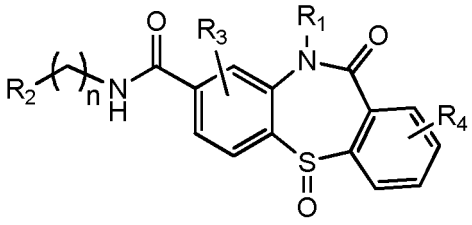
(Formula I)

In which any of the following conditions are met. Any of the following conditions can be combined so long as a stable compound results.

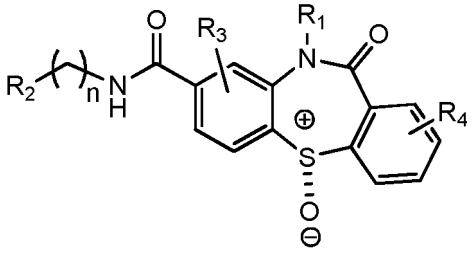
[0049] Formula II-IV, subformulae of Formula I, are included.



(Formula II)



(Formula III)



(Formula IV)

[0050] The variables, e.g., R_4-R_4 and n, may carry the values set forth in the Summary section or may carry any of the variables set forth below.

[0051] The disclosure includes embodiments in which R_1 carries any of the following values.

(i) R_1 is C_1-C_6alkyl, C_2-C_6alkenyl, or (C_3-C_7Cycloalkyl)C_0-C_2alkyl.
(ii) R_1 is C_1-C_6alkyl.

(iii) R_1 is methyl or ethyl, and R_3 and R_4 are both 0 substituents.

[0052] The disclosure includes embodiments in which R_3 and R_4 are both 0, 1, or 2 substituents independently chosen from halogen, hydroxyl, amino, cyano, C_1-C_2alkyl, C_1-C_2alkoxy, trifluoromethyl, difluoromethoxy, and trifluoromethoxy.

[0053] The disclosure includes embodiments in which n is 1, 2, or 3 and

is unsubstituted or substituted with one C_1-C_4alkyl substituent or 1 trifluoromethyl substituent and in which n is 1 or 2 and

is unsubstituted or substituted with one methyl substituent

[0054] The disclosure includes embodiments in which R_2 carries any of the following values.

(i) R_2 is C_3-C_7cycloalkyl, 5- or 6-membered heterocycloalkyl containing 1 or 2 heteroatoms selected from N, O, or S, phenyl, naphthyl, phenyl fused to a 5- or 6-membered heterocyclic ring containing 1 or 2 oxygen atoms, pyridyl, pyrimidinyl, pyrazinyl, thienyl, furanyl, pyrrolyl, or imidazolyl, each of which R_2 is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, (mono- and di-C_1-C_4alkylamino)C_0-C_2alkyl, C_1-C_4alkylthio, C_1-C_4alkylsulfonyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

(ii) R_2 is phenyl, naphthyl, benzo[d][1,3]dioxolyl, pyridyl, thienyl, furanyl, indolyl, imidazolyl, thiazolyl, pyrrolidinyl, piperidinyl, piperazinyl, pyrrolyl, morpholinyl, each which is substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, (mono- and di-C_1-C_4alkylamino)C_0-C_2alkyl, C_1-C_4alkylthio, C_1-C_4alkylsulfonyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

(iii)R_2 is phenyl, naphthyl, benzo[d][1,3]dioxolyl, pyridyl, thienyl, pyrrolidinyl, piperidinyl, piperazinyl, each which is substituted with one or more substituents independently chosen from halogen, hydroxyl, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, methylthio, methylsulfonyl, trifluoromethyl, and trifluoromethoxy.

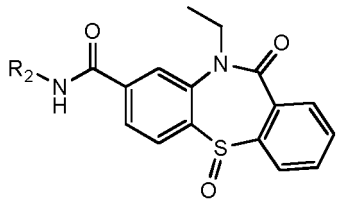
[0055] The disclosure also includes compounds of Formula III or IV and salts thereof in which R_1 is C_1-C_6alkyl or (C_3-C_7Cycloalkyl)C_0-C_2alkyl; R_3 and R_4 and both 0, 1, or 2 substituents independently chosen from halogen, hydroxyl, amino, cyano, C_1-C_2alkyl, C_1-C_2alkoxy, trifluoromethyl, difluoromethoxy, and trifluoromethoxy;
n is 1, 2, or 3 and

is unsubstituted or substituted with one C_1-C_4alkyl substituent or one trifluoromethyl substituent; and
R_2 is phenyl, naphthyl, benzo[d][1,3]dioxolyl, pyridyl, thienyl, furanyl, indolyl, imidazolyl, thiazolyl, pyrrolidinyl, piperidinyl, piperazinyl, pyrrolyl, morpholinyl, each which is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, (mono- and di-C_1-C_4alkylamino)C_0-C_2alkyl, C_1-C_4alkylthio, C_1-C_4alkylsulfonyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

[0056] The disclosure includes compounds of Formula III or IV and salts thereof, wherein R_1 is C_1-C_4alkyl;
R_3 and R_4 are both 0 substituents; n is 1, 2, or 3;

is unsubstituted or substituted with one methyl substituent; and
R_2 carries any of the definitions for R_2 set forth in this disclosure.

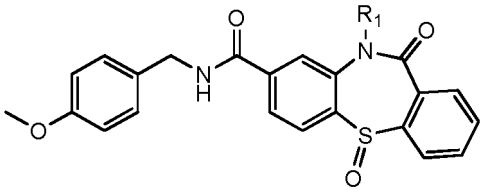
[0057] Also described are compounds and salts of Formula V:



(V).

In Formula V, R_2 may carry any of the definitions set forth herein. In certain embodiments R_2 is benzyl, 1-phenethyl, phenylethyl, or benzo[d][1,3]dioxol-5-ylmethyl, each of which is unsubstituted or substituted with one or more substituents chosen from thiomethyl, halogen, cyano, C_1-C_4alkyl, C_1-C_2methoxy, C_1-C_2alkylsulfonyl, trifluoromethyl, or trifluoromethoxy.

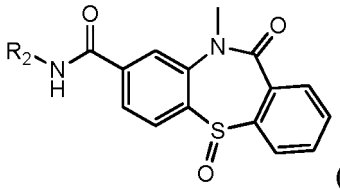
[0058] Also described are compounds and salts of Formula VI:



(VI).

In Formula VI, R_1 may carry any of the definitions set forth herein. In certain embodiments R_1 is methyl, ethyl, n-propyl, or benzyl.

[0059] Also described are compounds and salts of Formula VII:

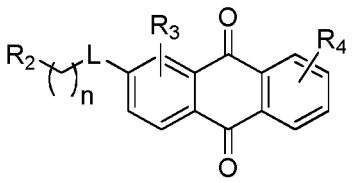


(VII).

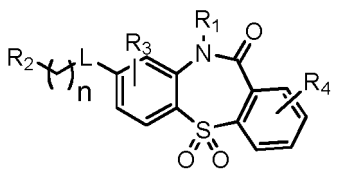
In Formula VI, R_2 may carry any of the definitions set forth herein. In certain embodiments R_2 is phenyl, benzyl, pyridylmethyl, thienylethyl, pyrrolidinylethyl, piperidinylethyl, phenyl substituted with halogen or methoxy, or benzyl substituted with halogen or methoxy.

[0060] In certain embodiments directed to compounds of Formula III or Formula IV and the salts thereof, R_2 is thienyl, which is unsubstituted or substituted with one or more substituents independently chosen from halogen, C_1-C_2alkyl, or C_1-C_2alkoxy, or R_2 is phenyl which is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, (mono- and di-C_1-C_4alkylamino)C_1-C_2alkyl, C_1-C_4alkylthio, C_1-C_4alkylsulfonyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

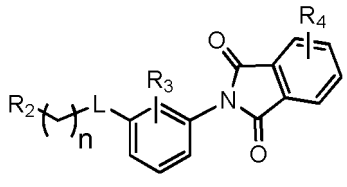
[0061] Also described are compounds of Formula (VIII), (IX), and (X) and the pharmaceutically acceptable salts thereof.



(VIII);



(IX);



(X).

In Formulas (VIII), (IX), and (X) each of R_1, R_2, R_3, R_4, L, and n may carry any of the definitions set forth in this disclosure for these variables.

PHARMACEUTICAL PREPARATIONS

[0062] Compounds disclosed herein can be administered as the neat chemical, but are preferably administered as a pharmaceutical composition. Accordingly, the disclosure provides pharmaceutical compositions comprising a compound or pharmaceutically acceptable salt of Formula I, together with at least one pharmaceutically acceptable carrier. The pharmaceutical composition/ combination may contain a compound or salt of Formula I as the only active agent or may be combined with one or more additional active agents. In certain embodiments the pharmaceutical composition is in a dosage form that contains from about 0.1 mg to about 2000 mg, from about 10 mg to about 1000 mg, from about 100 mg to about 800 mg, or from about 200 mg to about 600 mg of a compound of Formula I.

[0063] Compounds disclosed herein may be administered orally, topically, parenterally, by inhalation or spray, sublingually, transdermally, via buccal administration, or by other means routine in the art for administering pharmaceutical compositions. The pharmaceutical composition may be formulated as any pharmaceutically useful form, e.g., as an aerosol, a cream, a gel, a pill, a capsule, a tablet, a syrup, a transdermal patch, or an ophthalmic solution. Some dosage forms, such as tablets and capsules, are subdivided into suitably sized unit doses containing appropriate quantities of the active components, e.g., an effective amount to achieve the desired purpose.

[0064] Carriers include excipients and diluents and must be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the patient being treated. The carrier can be inert or it can possess pharmaceutical benefits of its own. The amount of carrier employed in conjunction with the compound is sufficient to provide a practical quantity of material for administration per unit dose of the compound.

[0065] Classes of carriers include, but are not limited to binders, buffering agents, coloring agents, diluents, disintegrants, emulsifiers, flavorants, glidants, lubricants, preservatives, stabilizers, surfactants, tableting agents, and wetting agents. Some carriers may be listed in more than one class, for example vegetable oil may be used as a lubricant in some formulations and a diluent in others. Exemplary pharmaceutically acceptable carriers include sugars, starches, celluloses, powdered tragacanth, malt, gelatin; talc, and vegetable oils. Optional active agents may be included in a pharmaceutical composition, which do not substantially interfere with the activity of the compound of the present invention.

[0066] The pharmaceutical compositions/ combinations can be formulated for oral administration. These compositions contain between 0.1 and 99 weight % (wt.%) of a compound of Formula I and usually at least about 5 wt.% of a compound of Formula I. Some embodiments contain from about 25 wt.% to about 50 wt. % or from about 5 wt.% to about 75 wt.% of the compound of Formula I.

METHODS OF TREATMENT

[0067] The disclosure describes methods of treating central nervous system disorders, including Tourette's syndrome, bipolar disorder, tardive dyskinesia, hyperprolactinemia, Huntington's chorea, psychosis, depression, or schizophrenia comprising administering an effective amount of a compound of Formula I to a patient having one of these disorders.

[0068] A compound of Formula I may be the only active agent administered (monotherapy) or may be combined with one or more other active agents (combination, adjunct, or augmentation therapy).

[0069] Also described is a method of treating depression comprising (i) diagnosing a patient as having depression and (ii) providing an effective amount of compound of Formula I to the patient, wherein the compound of Formula I is provided as the only active agent or is provided together with one or more additional active agents.

[0070] Psychosocial intervention may play an important role in treatment of any of central nervous system disorder. Psychosocial intervention includes cognitive-behavior therapy, dialectical-behavior therapy, interpersonal therapy, psychodynamic therapy, and group therapy.

[0071] The effective amount of a compound of Formula I can be an amount effective to decrease psychiatric symptoms. For example an effective amount of a compound of Formula I is an amount sufficient to decrease Tourette's symptoms or schizophrenia symptoms. Preferably the decrease in Tourette's symptoms or schizophrenia symptoms is a 50% or greater reduction of symptoms identified on symptom rating scale for these disorders. For example an effective amount

may be an amount sufficient to decrease the patient's score on a psychiatric symptoms rating scale such as the Brief Psychiatric Rating Scale, the Clinical Global Impression, or the Positive and Negative Syndrome Scale.

[0072] EXAMPLES - these are Examples of the claimed invention or otherwise.

ABBREVIATIONS

[0073]

AcOH Acetic acid
CDI 1,1'-carbonyldiimidazole
DMF Dimethylformamide
DIPEAN,N-Diisopropylethylamine
HATU O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
THF tetrahydrofuran

GENERAL METHODS FOR CHEMISTRY

[0074] All solvents were of anhydrous quality purchased from Aldrich Chemical Co., and used as received. Commercially available starting materials and reagents were purchased from Aldrich, TCI and Acros and were used as received.

[0075] Analytical thin layer chromatography (TLC) was performed with Sigma Aldrich TLC plates (5 × 20 cm, 60 Å, 250 μm). Visualization was accomplished by irradiation under a 254 nm UV lamp. Chromatography on silica gel was performed using forced flow (liquid) of the indicated solvent system on Biotage KPSil pre-packed cartridges and using the Biotage SP-1 automated chromatography system. ^{1}H

[0076] NMR spectra were recorded on a Varian Inova 400 MHz spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$ 7.27 ppm, DMSO-d_6 2.49 ppm, for ^{1}H NMR). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, quin = quintet, br = broad, m = multiplet), coupling constants, and number of protons.

[0077] Low resolution mass spectra (electrospray ionization) were acquired on an Agilent Technologies 6130 quadrupole spectrometer coupled to an Agilent Technologies 1200 series HPLC. The HPLC retention time were recorded through standard gradient 4% to 100% acetonitrile (0.05% TFA) over 7 minutes using Luna C_{18} (3 μm, 3 mm × 75 mm) column with a flow rate of 0.800 mL/min. High resolution mass spectral data were collected in-house using an Agilent 6210 time-of-flight mass spectrometer coupled to an Agilent Technologies 1200 series HPLC system. If needed, products were purified via a Waters preparative HPLC equipped with a Phenomenex Luna C_{18} reverse phase (5 μm, 30 mm × 75 mm) column having a flow rate of 45 mL/min. The mobile phase was a mixture of acetonitrile (0.1% TFA) and H_2O (0.1% TFA) for acidic condition and a mixture of acetonitrile and H_2O (0.1% NH_4OH) for basic condition.

[0078] Samples were analyzed for purity on an Agilent 1200 series LCMS equipped with a Luna C_{18} reverse phase (3 μm, 3 mm × 75 mm) column having a flow rate of 0.800 mL/min over a 7.0 minutes gradient and a run time of 8.5 minutes. Purity of final compounds was determined to be > 95%, using a 3 μL injection with quantitation by AUC at 220 and 254 nm (Agilent diode array detector).

[0079] General Protocol A. A mixture of acid (0.095 mmol, 1.0 equiv.) and amine (0.19 mmol, 2 equiv.) in DMF (1.00 mL) was treated at room temperature with EDC (0.19 mmol, 2.0 equiv.) and DMAP (0.19 mmol, 2.0 equiv). The reaction mixture was stirred at room temperature for overnight. The crude material was purified by preparative HPLC to give the final product.

[0080] General Protocol B. A solution of acid (0.16 mmol, 1.0 equiv.) in DMF (2.00 mL) was treated at room temperature with HATU (0.32 mmol, 2.0 equiv.) and DIPEA (0.32 mmol, 2.0 equiv). The mixture was stirred at room temperature for 5 min, and then amine (0.32 mmol, 2.0 equiv.) was added. The reaction mixture was stirred at room temperature for overnight. The crude material was purified by preparative HPLC to give the final product.

EXAMPLE 1. PRIMARY HTS OF SYTRAVON LIBRARY AND CONFIRMATORY SCREEN: D_2 CA^{2+} SCREEN ASSAY

[0081] For the primary screen, a calcium accumulation assay was executed using a cell line which stably expressed the D_2 DAR under control of Tetracycline-Regulated Expression (HEK293 T-REx™), as well as chimeric G-protein (G_{q15}) to allow coupling of the D_2 DAR to calcium release. In this system, D_2 DAR gene expression is induced by addition of Tet to the cells prior to the assay and intracellular Ca^{2+} release was detected with a specific Ca^{2+} fluorescent dye.

[0082] The resting concentration of calcium ions (Ca^{2+}) in the cells' cytoplasm is normally maintained in the range of 10-100 nM. To maintain this low concentration, Ca^{2+} is actively pumped from the cytosol to the extracellular space and into the endoplasmic reticulum (ER), and sometimes into the mitochondria. Signaling occurs when the cell is stimulated to release Ca^{2+} from intracellular stores. The most common signaling pathway that increases cytoplasmic calcium

concentration is the phospholipase C (PLC) pathway. In the engineered cell line used for screening, dopamine stimulation of the D_2 DAR activates the chimeric G_{q15} G-protein, which in turn acts on PLC which hydrolyses the membrane phospholipid PIP2 to form inositol trisphosphate (IP3) and diacylglycerol (DAG). IP_3 diffuses to the ER, binds to its receptor (IP3 receptor), which is a Ca^{2+} channel and, thus, releases Ca^{2+} from the ER to the cytosol. To measure this cytosolic Ca^{2+} accumulation, we used the Screen Quest™ Fluo-8 Calcium Assay Kit (AAT Bioquest, Sunnyvale, CA). Acetoxymethyl (AM) esters bound to Fluo-8™ dye are non-polar molecules that easily cross live cell membranes transporting the dye inside the cell, and are then rapidly hydrolyzed by cellular esterases inside live cells. As Fluo-8™ is freed from AM esters, it binds to Ca^{2+} and emits a fluorescent signal at 514 nm that escalates with increasing cytosolic Ca^{2+}. To measure this calcium flux signal, we used the Functional Drug Screening System (FDSS) (Hamamatsu, Japan), a high throughput screening device that allows optical detection of signal transmissions within living cells in a time-resolving fashion.

[0083] The cells were plated in DMEM media with High Glucose (Gibco, #10564), 10% FBS, 1xNEAA, and Pen/Strep. 24 hr after thawing, selective antibiotics Hygromycin B (10 μg/mL), Puromycin (2 μg/mL) and Blasticidin (15 μg/mL) were added to the media for growing and passaging the cells. Cells were split and harvested for the experiment at ~90% confluence with TrypLE dissociation reagent and seeded at 2,100 cells, 3 μL/well in complete media without selective antibiotics with added Tet (1 μg/mL) using a MultiDrop Combi dispenser (Thermo Scientific, Logan, UT) onto 1,536-well tissue culture treated, black-walled, clear bottom plates (Greiner Bio-One North America).

[0084] Quest Fluo-8™ calcium reagent was freshly prepared prior to adding to the cells (lyophilized Fluo-8™ dye provided with the kit was re-suspended in 200 μL DMSO as a 500x stock and stored at -20 °C). 2 μL/well of Quest Fluo-8™ calcium dye diluted in HBSS + 10 mM HEPES buffer (for every 10 mL buffer, 1 mL of 10x quencher provided in the kit and 20 μL of 500x DMSO stock dye were added) was added to cells with a Multi-Drop Combi (ThermoScientific) and incubated for 45-90 min in the dark at ambient temperature. Then, the plates were introduced into the FDSS where they were pinned with 23 nL of test compound or dopamine controls and were read by FDSS in non-stimulated mode for 180 sec for detection of agonists. At that time point, 1 μL/well dopamine at 1 nM (EC_{20}) or 14 nM (EC_{80}) final concentration was added by the FDSS pipette head followed by 120 sec kinetic read for detection/recording of potentiators or antagonists stimulation.

[0085] Table 1 summarizes the protocol for the Ca^{2+} assay.

TABLE 1. Ca^{2+} Assay Protocol

Sequence	Parameter	Value	Description
1	D_2 T-REx HEK293	3 μL	2,100 cells/well in complete media with Tet
2	Time	20-24 hr	Incubate at 30 °C, 5% CO_2
3	Reagent	2 μL	Calcium dye(500 ×) with quencher (10 ×) in HBSS+10 mM HEPES buffer
4	Time	45-90 min	Room temp dark
5	Compound/Controls	23 nL	Transfer libraries/dopamine controls: 10 mM as EC_{100} & dose response 1:2 using FDSS pintool
6	Time	180 sec kinetic	37 °C, FDSS fluorescent read
7	Ligand	1 μL	Dopamine EC_{20} (1 nM) or EC_{80} (14 nM)
8	Time	120 sec kinetic	37 °C, FDSS fluorescent read

[0086] The cell line HEK293 D_2 T-REx™ used in the primary screen was also used to confirm activity of the active compounds selected from the primary qHTS and synthesized analogs on 1,536-well format following the same protocol as described above for the primary screen.

EXAMPLE 2. D_2 BETA-ARRESTIN FUNCTIONAL ASSAY

[0087] For a secondary-screen and selectivity assays, DAR PathHunter® β-arrestin GPCR cell lines from DiscoveRx

(Fremont, CA). In this) were used. In the D_2 Receptor PathHunter® β-arrestin GPCR cell line, the D_2 GPCR receptor (DAR) is overexpressed and fused with a small 42-amino acid fragment of β-galactosidase called ProLink™ on a CHO cellular background expressing a fusion protein of β-arrestin and a larger *N*-terminal deletion mutant of β-galactosidase ("enzyme acceptor"). When DAR is activated by dopamine, it stimulates binding of β-arrestin to the ProLink-tagged DAR and the two complementary parts of β-galactosidase form a functional enzyme. When substrate (PathHunter® Detection reagent) is added, β-galactosidase hydrolyzes it and generates a chemiluminescent signal.

[0088] D_2 Receptor PathHunter® β-arrestin cells were seeded at 2,100 cells/well in 3 μL/well media (DiscoveRx Plating Reagent 2) with MultiDrop Combi dispenser (Thermo Scientific, Logan, UT) onto white tissue culture treated 1,536-well Aurora plates (Brooks Automation, Chelmsford, MA) and allowed to attach overnight at 37 °C, 5% CO_2. Next, 23 nL/well of compound solutions in DMSO were added with a pintool transfer (Kalypsis, San Diego, CA). The cells were stimulated by compounds for 90 min at 37 °C, 5% CO_2, after which 1.5 μL/well of DiscoveRx detection reagent was added with BioRAPTR FRD dispenser. The detection reagent was prepared by mixing of Galacton Star Substrate, Emerald II solution and PathHunter buffer (supplied by the assay kit) together at a 1:5:19 proportion just prior to dispensing. The plates were incubated at ambient temperature for 1 hr, and the luminescent signal was read on a ViewLux plate reader (PerkinElmer, Waltham, MA). Table 2 summarizes the protocol for the β-arrestin assay.

TABLE 2. Protocol for the β-Arrestin Assay

Sequence	Parameter	Value	Description
1	Cells	3 μL	2,100 cells/well
2	Time	16-20 hr	Incubate at 37 °C and 5% CO_2
3	Ligand	1 μL	1.5 μM dopamine in HBSS+10 mM HEPES+SMB
4	Reagent	23 nL	Compound library, dopamine as control (in DMSO)
5	Time	90 min	Incubate at 37 °C and 5% CO_2
6	Detection Reagent	1.5 μL	1:5:19 Galacton Star Substrate: Emerald II solution: PathHunter buffer
7	Time	60 min	Room temperature incubation
8	Detector	30 sec	Luminescent settings, ViewLux plate reader

EXAMPLE 3. D_2 BINDING ASSAY

[0089] Compounds were tested for differences in affinity between three dopamine receptor subtypes using radiolabeled ligand binding assays. The first assay determined the *K*i value of the compounds for the D_2 DAR subtype using stable HEK cell lines expressing the D_{2L} human dopamine receptors (Codex Biosciences, Gaithersburg, MD). Cells were cultured in Dulbecco's modified Eagle's Medium containing 10% FBS, 1,000 units/mL Penicillin, 1,000 mg/mL Streptomycin, 100 mM Sodium Pyruvate, 1 μg/mL Gentamicin, and 250 mg/mL G418. All cells were maintained at 37 °C in 5% CO_2 and 90% humidity. For radioligand binding assays, cells were removed mechanically using calcium and magnesium-free Earle's Balanced Salt Solution (EBSS(-)). Intact cells were collected by centrifugation and then lysed with 5 mM Tris-HCl and 5 mM $MgCl_2$ at pH 7.4 in a glass homogenizer. Homogenates were centrifuged at 20,000 x g for 30 minutes. The membranes were re-suspended in EBSS (pH 7.4) and protein concentration was determined using a Bradford assay according to the manufacturer's recommendations (Bio-Rad). Membranes were diluted to 24 mg/mL. It was determined in preliminary experiments that this protein concentration gave optimal binding with minimal ligand depletion. Membrane preparations were incubated for 90 min at room temperature with various concentrations of radioligand in a reaction volume of 250 μL EBSS containing 200 mM sodium metabisulfite. Non-specific binding was determined in the presence of 4 μM (+)-butaclamol. Bound ligand was separated from unbound by filtration through GF/C filters using a PerkinElmer cell harvester with ice cold EBSS (4 washes) and quantified on a Top-count (PerkinElmer) after addition of scintillation solution. Saturation experiments generated a K_d value of 0.2 nM and a B_{max} of ~4,200 fmol/mg for [^{3}H]-methylspiperone binding to D_2 receptors. In order to determine the affinity of a given compound for a receptor type, competition-binding assays were performed. For these assays the reaction mixture was incubated with a single concentration of radiolabeled ligand (0.2 nM [^{3}H]methylspiperone) and various concentrations of competing compound. Reactions were incubated, terminated, and quantified as indicated above. K_i values of compounds were determined from observed IC_{50} values using the Cheng-Prussoff equation.

[0090] The protocol for the D_2 Binding Assay is summarized in Table 3.

TABLE 3. D_2 Binding Assay Protocol			
Sequence	Parameter	Value	Description
1	Cells	25 mL	2×10^7 cells/flask
2	Time	24 hr	Incubate at 37 °C and 5% CO_2
3	Reagent	10 mL	EBSS (-)
4	Time	10 min	Room temperature
5	Centrifuge	900 x g	Pellet cells
6	Lysis	6 mL	Re-suspend and homogenize in lysis buffer
7	Centrifuge	20,000 x g	Pellet homogenate
8	Buffer	10 mL	Re-suspend in EBSS to appropriate protein concentration
9	Reagent	25 μL	Buffer/Butaclamol/Test compound per assay tube
10	Reagent	125 μL	Radioligand per assay tube
11	Lysate	100 μL	Membrane preparation per assay tube
12	Time	90 min	Incubate at room temperature with shaking
13	Filter	4 washes	Filter membranes onto GF/C filter plates
14	Reagent	50 μL	Perkin Elmer scintillation cocktail
15	Detector	Scintillation	Perkin Elmer - Top count

EXAMPLE 4. D_3 BETA -ARRESTIN FUNCTIONAL ASSAY

[0091] A D_3 PathHunter® β-arrestin cell line from DiscoveRx (Fremont, CA) was used to determine the functional selectivity of the compounds for D_2 *versus* D_3 receptor antagonism. A CHO cell line was engineered to overexpress D_3 dopamine receptor (DAR) and fused with a small 42-amino acid fragment of β-gal called ProLink™. In addition, these cells stably express a fusion protein of β-arrestin and a larger *N*-terminal deletion mutant of β-galactosidase ("enzyme acceptor"). When DAR is activated by dopamine, it stimulates binding of β-arrestin to ProLink-tagged DARs, and the two complementary parts of β-galactosidase form a functional enzyme. When substrate (PathHunter® Detection reagent) is added, β galactosidase hydrolyzes it and generates a chemiluminescent signal.

[0092] For the 1,536-well assay, D_3 PathHunter® β-arrestin cells were seeded at 2,100 cells/well in 3 μL/well media (DiscoveRx Plating Reagent 2) with MultiDrop Combi dispenser (Thermo Scientific, Logan, UT) onto white tissue culture treated 1,536-well Aurora plates (Brooks Automation, Chelmsford, MA) and allowed to attach overnight at 37 °C, 5% CO_2. Next, 23 nL/well of compound solutions in DMSO were added with a pintool transfer (Kalypsis, San Diego, CA). The cells were stimulated by compounds for 90 minutes at 37 °C, 5% CO_2, after which 1.5 μL/well of DiscoveRx detection reagent was added with BioRAPTR FRD dispenser. The detection reagent was prepared by mixing of Galacton Star Substrate, Emerald II solution, and PathHunter buffer (supplied by the assay kit) together at a 1:5:19 proportion just prior to dispensing. The plates were incubated at ambient temperature for 1 h, and the luminescent signal was read on ViewLux plate reader (PerkinElmer, Waltham, MA).

[0093] The D_3 β-arrestin assay protocol is summarized in Table 4.

TABLE 4.			
Sequence	Parameter	Value	Description
1	Cells	3 μL	2,100 cells/well
2	Time	16-20 hr	Incubate at 37 °C and 5% CO_2
3	Ligand	1 μL	12.5 nM dopamine in HBSS+10 mM HEPES+SMB
4	Reagent	23 nL	Compound library, dopamine as control (in DMSO)
5	Time	90 min	Incubate at 37 °C and 5% CO_2

(continued)

TABLE 4.			
Sequence	Parameter	Value	Description
6	Detection Reagent	1.5 μL	1:5:19 Galacton Star Substrate: Emerald II solution: PathHunter buffer
7	Time	60 min	Room temperature incubation
8	Detector	30 sec	Luminescent settings, ViewLux plate reader

EXAMPLE 5. D_3 BINDING ASSAY

[0094] Compounds were counter screened for affinity for the D_3 dopamine receptor. This was accomplished by determining the K_i values for the compounds using stable (HEK293 based) cell lines expressing the D_3 human dopamine receptors (Codex Biosciences, Gaithersburg, MD). Cells were cultured in Dulbecco's modified Eagle's Medium containing 10 % FBS, 1,000 units/mL Penicillin, 1,000 mg/mL Streptomycin, 100 mM Sodium Pyruvate, 1 μg/mL Gentamicin, and 250 mg/mL G418. All cells were maintained at 37 °C in 5% CO_2 and 90% humidity. For radioligand binding assays, cells were removed mechanically using calcium and magnesium-free Earle's Balanced Salt Solution (EBSS(-)). Intact cells were collected by centrifugation and then lysed with 5 mM Tris-HCl and 5 mM $MgCl_2$ at pH 7.4 in a glass homogenizer. Homogenates were centrifuged at 20,000 x g for 30 min. The membranes were re-suspended in EBSS (pH 7.4), and protein concentration was determined using a Bradford assay according to the manufacturer's recommendations (Bio-Rad). Membranes were diluted to 80 mg/mL, the predetermined optimal protein concentration for binding but minimal ligand depletion. Membrane preparations were incubated for 90 min at room temperature with various concentrations of radioligand in a reaction volume of 250 μL EBSS containing 200 mM sodium metabisulfite. Non-specific binding was determined in the presence of 4 μM (+)-Butaclamol. Bound ligand was separated from unbound by filtration through GF/C filters using a PerkinElmer cell harvester with ice cold EBSS (4 washes) and quantified on a Top-count (PerkinElmer) after addition of scintillation solution. Saturation experiments generated a K_d value of 0.125 nM and a Bmax of ~600 fmol/mg for [^{3}H]-methylspiperone binding to D_3 receptors. In order to determine the affinity of a given compound for a receptor type, competition-binding assays were performed. For these assays the reaction mixture was incubated with a single concentration of radiolabeled ligand (0.5 nM [^{3}H]methylspiperone) and various concentrations of competing compound. Reactions were incubated, terminated, and quantified as indicated above. K_i values of compounds were determined from observed IC_{50} values using the Cheng-Prussoff equation.

[0095] The D_3 binding assay protocol is summarized in Table 5.

TABLE 5			
Sequence	Parameter	Value	Description
1	Cells	25 mL	2×10^7 cells/flask
2	Time	24 hr	Incubate at 37 °C and 5% CO_2
3	Reagent	10 mL	EBSS (-)
4	Time	10 min	Room temperature
5	Centrifuge	900 x g	Pellet cells
6	Lysis	6 mL	Re-suspend and homogenize in lysis buffer
7	Centrifuge	20,000 x g	Pellet homogenate
8	Buffer	10 mL	Re-suspend in EBSS to appropriate protein concentration
9	Reagent	25 μL	Buffer / Butaclamol/Test compound per assay tube
10	Reagent	125 μL	Radioligand per assay tube
11	Lysate	100 μL	Membrane preparation per assay tube
12	Time	90 min	Incubate at room temperature with shaking
13	Filter	4 washes	Filter membranes onto GF/C filter plates
14	Reagent	50 μL	Perkin Elmer scintillation cocktail

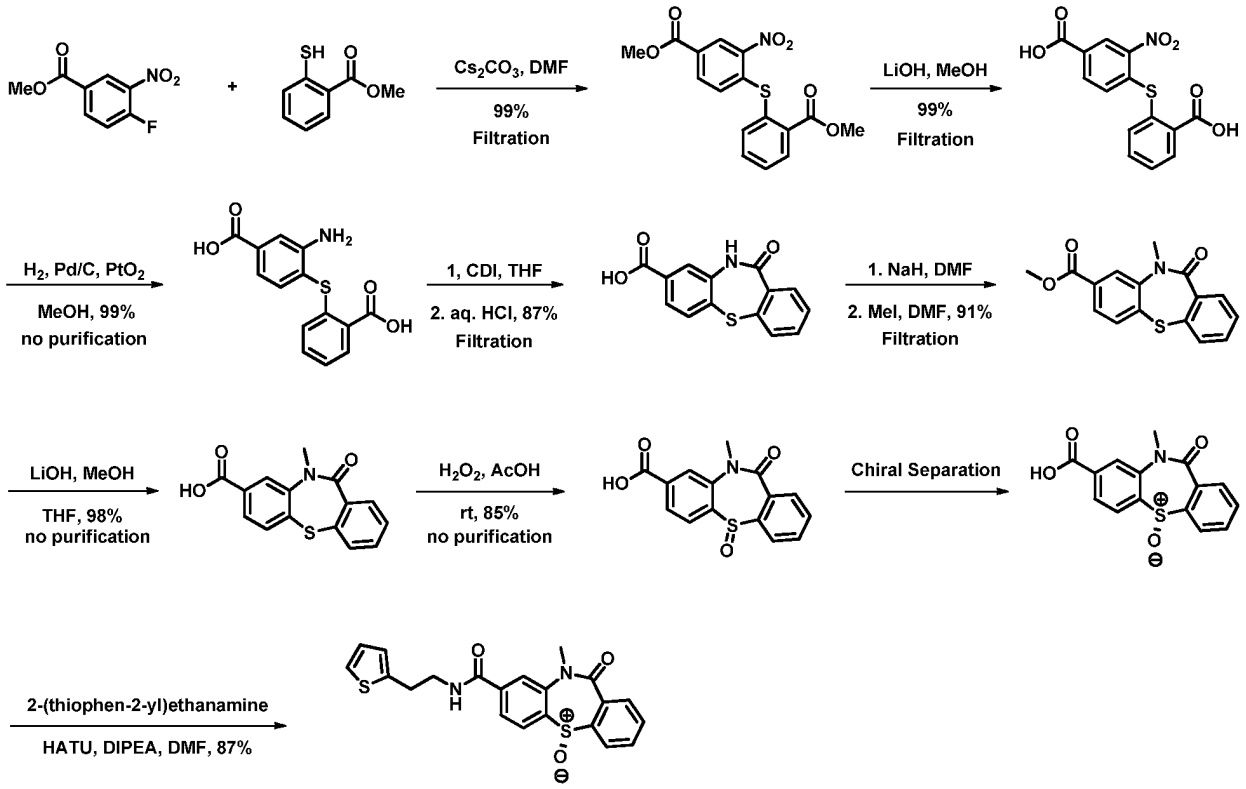
(continued)

TABLE 5			
Sequence	Parameter	Value	Description
15	Detector	Scintillation	Perkin Elmer - Top count

EXAMPLE 6. SYNTHESIS OF 10-METHYL-11-OXO-*N*-(2-(THIOPHEN-2-YL)ETHYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-(*S*)-OXIDE

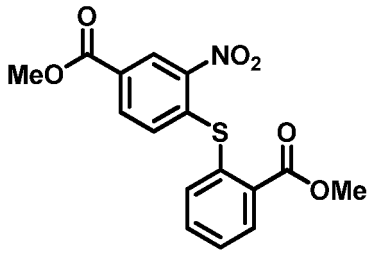
[0096]

SYNTHETIC SCHEME



Step 1. Preparation of Methyl 4-(2-(methoxycarbonyl)phenylthio)-3-nitrobenzoate

[0097]

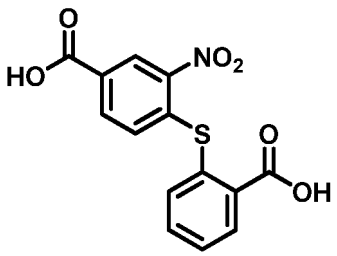


[0098] A solution of methyl 4-fluoro-3-nitrobenzoate (12.1 g, 60.9 mmol) and methyl 2-mercaptobenzoate (9.21 mL, 66.9 mmol) in DMF (6.00 mL) was treated with Cs_2CO_3 (19.8 g, 60.9 mmol) at room temperature. The reaction mixture was stirred at 40 °C for 4 hr and then cooled to room temperature. Ice water was added to induce the precipitation. The

precipitate was filtered, washed with water, and dried to give 21.0 g (99%) of the title compound as a yellow solid which was used directly in the next reaction without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.63 (d, *J*=2.0 Hz, 1 H), 8.04 (dd, *J*=8.4, 1.8 Hz, 1 H), 7.87 - 7.99 (m, 1 H), 7.57 - 7.77 (m, 3 H), 7.05 (d, *J*=8.6 Hz, 1 H), 3.88 (s, 3 H), 3.71 (s, 3 H); LCMS RT = 6.19 min, *m/z* 365.0 [M+Na$^+$]; HRMS (ESI) *m/z* calcd for $C_{16}H_{143}NNaO_6S$ [M+Na$^+$] 371.0387, found 371.0393.

Step 2. Preparation of 4-(2-Carboxyphenylthio)-3-nitrobenzoic acid

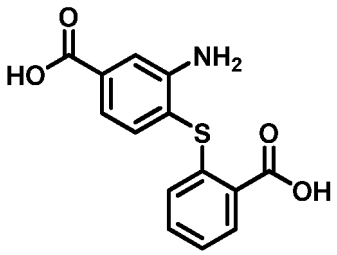
[0099]



[0100] A solution of methyl 4-(2-(methoxycarbonyl)phenylthio)-3-nitrobenzoate (21.0 g, 60.5 mmol) in THF (150 mL) and water (150 mL) was treated at room temperature with LiOH (14.5 g, 605 mmol). The reaction mixture was stirred at 60 °C for 2 hr. The organic solvent was removed and the aqueous solution was washed with EtOAc and acidified with 2 N HCl until pH = ~2. The yellow precipitate was filtered, washed with water, and dried to give 19.1 g (99%) of the title compound as a yellow solid which was used directly in the next reaction without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.53 (br. s., 1 H), 13.27 (br. s., 1 H), 8.58 (d, *J*=1.6 Hz, 1 H), 8.01 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.85 - 7.95 (m, 1 H), 7.48 - 7.68 (m, 3 H), 7.07 (d, *J*=8.6 Hz, 1 H); LCMS RT = 4.73 min, *m/z* 341.9 [M+Na$^+$]; HRMS (ESI) *m/z* calcd for $C_{14}H_9NNaO_6S$ [M+Na$^+$] 342.0043, found 342.0047.

Step 3. Preparation of 3-Amino-4-(2-carboxyphenylthio)benzoic acid

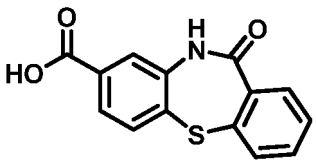
[0101]



[0102] A solution of 4-(2-carboxyphenylthio)-3-nitrobenzoic acid (8.70 g, 27.2 mmol) in MeOH (300 mL) was treated at room temperature with platinum (IV) oxide (300 mg, 1.32 mmol) and Pd/C (10%, 600 mg, 5.64 mmol). A balloon containing H_2 was connected to the flask and the reaction flask was repeatedly evacuated and refilled with H_2. After 16 hr, additional Pd/C (10%, 600 mg, 5.64 mmol) was added and the reaction mixture was stirred under H_2 balloon for an additional 32 hr. The reaction mixture was filtered through a pad of celite and concentrated to give 7.80 g (99%) of the title compound as a grey-yellow solid which was used directly in the next reaction without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.99 (br. s., 2 H), 7.92 (dd, *J*=7.8, 1.6 Hz, 1 H), 7.42 (d, *J*=1.6 Hz, 1 H), 7.37 (d, *J*=7.8 Hz, 1 H), 7.31 - 7.36 (m, 1 H), 7.18 (td, *J*=7.6, 1.2 Hz, 1 H), 7.13 (dd, *J*=8.0, 1.8 Hz, 1 H), 6.61 (dd, *J*=8.2, 0.8 Hz, 1 H), 5.40 (br. s., 2 H); LCMS RT = 4.25 min, *m/z* 290.0 [M+H$^+$]; HRMS (ESI) *m/z* calcd for $C_{14}H_{12}NO_4S$ [M+H$^+$] 290.0482, found 290.0486.

Step 4. Preparation of 11-Oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxylic acid

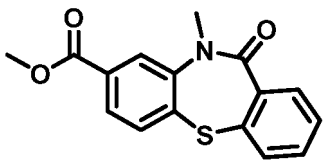
[0103]



[0104] A solution of 3-amino-4-(2-carboxyphenylthio)benzoic acid (4.76 g, 16.5 mmol) in THF (100 mL) was treated at 0 °C with 1,1'-carbonyldiimidazole (CDI) (10.7 g, 65.8 mmol) via several portions. The reaction mixture was warmed to room temperature and stirred at room temperature overnight. The reaction mixture was poured into 140 mL of ice water containing concentrated HCl (20.0 mL) and stirred for 1 hr. The white precipitate was filtered, washed with water, and dried to give 3.89 g (87%) of the title compound as a white solid which was used directly in the next reaction without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.20 (br. s., 1 H), 10.79 (s, 1 H), 7.76 (d, *J*=1.2 Hz, 1 H), 7.62 - 7.70 (m, 3 H), 7.41 - 7.57 (m, 3 H); LCMS RT = 4.55 min, *m*/*z* 271.9 [M+H$^+$]; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{10}NO_3S$ [M+H$^+$] 272.0376, found 272.0376.

Step 5. Methyl 10-methyd-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxydate

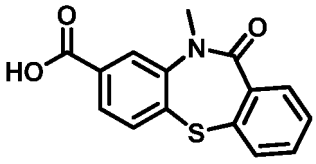
[0105]



[0106] A solution of 11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxylic acid (200 mg, 0.74 mmol) in DMF (5.00 mL) was treated at 0 °C with NaH (295 mg, 7.37 mmol). The reaction mixture was warmed to room temperature and stirred at room temperature for 1 hr. Then, a solution of methyl iodide (0.46 mL, 7.37 mmol) in DMF (2.00 mL) was added dropwise to the mixture. The reaction mixture was stirred at room temperature for 1.5 hr. Water was carefully added and the aqueous layer was washed with EtOAc. The aqueous layer was acidified with HCl to induce the precipitation which was filtered, washed, and dried to give 200 mg (91%) of the title compound as a yellow solid which was used directly in the next reaction without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (d, *J*=1.2 Hz, 1 H), 7.68 - 7.79 (m, 2 H), 7.59 - 7.66 (m, 1 H), 7.47 - 7.54 (m, 1 H), 7.37 - 7.45 (m, 2 H), 3.83 (s, 3 H), 3.52 (s, 3 H); LCMS RT = 5.59 min, *m*/*z* 300.0 [M+H$^+$]; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{14}NO_3S$ [M+H$^+$] 300.0689, found 300.0693.

Step 6. Preparation of 10-Methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxylic acid

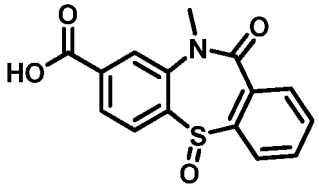
[0107]



[0108] A solution of methyl 10-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxylate (150 mg, 0.50 mmol) in THF (3.00 mL), MeOH (1.50 mL) and water (0.50 mL) was treated at room temperature with LiOH (120 mg, 5.01 mmol). The reaction mixture was stirred at room temperature for 1 hr, diluted with water, and acidified with HCl. The aqueous mixture was extracted with 20% of MeOH in dichloromethane. The organic layer was separated, dried and concentrated to give 140 mg (98%) of the title compound as a grey solid which was used directly in the next reaction without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 13.31 (br. s., 1 H), 7.98 (d, *J*=1.2 Hz, 1 H), 7.67 - 7.76 (m, 2 H), 7.59 - 7.66 (m, 1 H), 7.47 - 7.54 (m, 1 H), 7.35 - 7.45 (m, 2 H), 3.52 (s, 3 H); LCMS RT = 4.76 min, *m*/*z* 286.0 [M+H$^+$]; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{12}NO_3S$ [M+H$^+$] 286.0532, found 286.0536.

Step 7. Preparation of 10-Methyl-11-oxo-10,11-dihydrodibenzo(b,f)(1,4)thiazepine-8-carboxylic acid 5-oxide

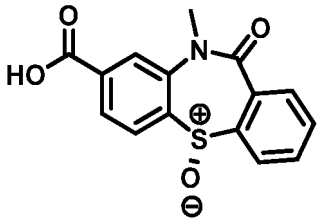
[0109]



[0110] A suspension of 10-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxylic acid (660 mg, 2.31 mmol) in acetic acid (18.8 mL) was treated at room temperature with H_2O_2 (5.91 mL, 30%, 57.8 mmol) for 8 hr. Upon completion, the reaction mixture was poured into a cold saturated solution of $Na_2S_2O_3$ in water and stirred at room temperature for 3 hr. The mixture was then extracted with 20% of MeOH in dichloromethane. The organic layer was separated, dried, and concentrated to give 595 mg (85%) of the title compound as a white solid containing ~ 5% of dioxide as a by-product. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.00 (d, *J*=1.2 Hz, 1 H), 7.96 (dd, *J*=8.2, 1.6 Hz, 1 H), 7.62 - 7.76 (m, 4 H), 7.52 - 7.59 (m, 1H), 3.53 (s, 3 H); LCMS RT = 4.02 min, *m*/*z* 302.0 [M+H$^+$]; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{12}NO_4S$ [M+H$^+$] 302.0482, found 302.0486.

Step 8. 10-Methyd-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxydic acid 5-(S)-oxide

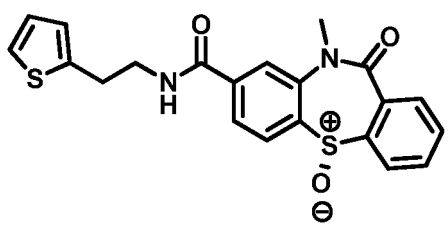
[0111]



[0112] The title enantiomerically pure compound was purified to > 98% purity using supercritical fluid chromatography (SFC) preparative systems at Lotus Separations, LLC (Princeton, NJ, USA). For preparative separation, an IC (2 x 15 cm) column was used with an eluent of 40% methanol (0.1% DEA)/CO_2, 100 bar. Flow rate was 60 mL/min and detection wavelength was 220 nm. For analytical separation, an IC (15 x 0.46 cm) column was used with an eluent of 40% methanol/CO_2, 100 bar. Flow rate was 3 mL/min and detection wavelengths were 220 and 280 nm. Retention time was 3.42 min. Retention time for *R*-configuration enantiomer was 2.40 min. The material was used directly in the next coupling reaction.

Step 9. Preparation of 10-Methyl-11-oxo-N-(2-(thiophen-2-yl)ethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-(S)-oxide (Compound 55)

[0113]



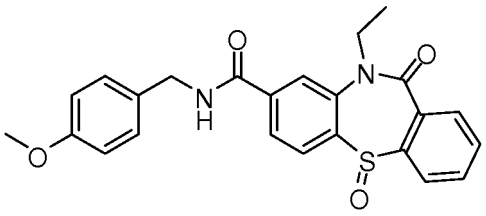
[0114] A solution of 10-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxylic acid 5-(*S*)-oxide (100 mg, 0.332 mmol) in DMF (5.00 mL) was treated at room temperature with HATU (139 mg, 0.365 mmol) and diisopropylethylamine (0.174 mL, 0.996 mmol) followed by 2-(thiophen-2-yl)ethanamine (84.0 mg, 0.664 mmol). The reaction mixture

was stirred at room temperature for 3 h and poured into ice water. The white precipitate was filtered and dried to give a white solid, which was purified via silica gel chromatography using a gradient of 10-100% of EtOAc in hexanes to give 118 mg (87%) of the title compound as a white solid.

[0115] LC-MS Retention Time: t_1 (Method 1) = 5.348 min; t_2 (Method 2) = 3.188 min; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.76 (t, *J*=5.7 Hz, 1 H), 7.94 (d, *J*=2.0 Hz, 1 H), 7.86 (dd, *J*=8.2, 2.0 Hz, 1 H), 7.69 - 7.77 (m, 2 H), 7.67 (d, *J*=8.2 Hz, 2 H), 7.51 - 7.60 (m, 1 H), 7.31 (dd, *J*=5.1, 1.2 Hz, 1 H), 6.92 (dd, *J*=5.1, 3.1 Hz, 1 H), 6.83 - 6.90 (m, 1 H), 3.55 (s, 3 H), 3.43 - 3.52 (m, 2 H), 3.02 (t, *J*=7.0 Hz, 2 H); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm 13C NMR (101 MHz, DMSO-d_6) δ ppm 165.16, 165.10, 147.66, 145.98, 141.75, 137.87, 137.02, 132.92, 131.69, 131.23, 128.20, 127.39, 126.51, 125.70, 124.57, 124.43, 121.05, 119.40, 41.55, 38.03, 29.49; HRMS (ESI) *m*/*z* $(M+H)^+$ calcd. for $C_{21}H_{19}N_2O_3S_2$ [$M+H^+$] 411.0832, found 411.0831.

EXAMPLE 7. 10-ETHYL-*N*-(4-METHOXYBENZYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 1)

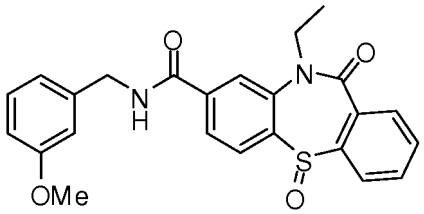
[0116]



[0117] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.08 (t, *J*=6.0 Hz, 1 H), 8.00 (d, *J*=1.4 Hz, 1 H), 7.92 (dd, *J*=8.1, 1.7 Hz, 1 H), 7.60 - 7.78 (m, 4 H), 7.55 (ddd, *J*=7.9, 7.0, 1.4 Hz, 1 H), 7.16 - 7.25 (m, 2 H), 6.81 - 6.88 (m, 2 H), 4.56 (dq, *J*=14.0, 7.1 Hz, 1 H), 4.26 - 4.45 (m, 2 H), 3.70 - 3.80 (m, 1 H), 3.69 (s, 3 H), 1.18 (t, *J*=7.1 Hz, 3 H); LCMS RT = 5.22 min, *m*/*z* 435.1 [$M+H^+$]; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{23}N_2O_4S$ [$M+H^+$] 435.1373, found 435.1371.

EXAMPLE 8. 10-ETHYL-*N*-(3-METHOXYBENZYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 2)

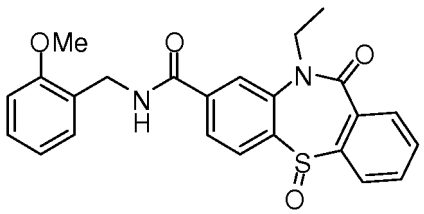
[0118]



[0119] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.13 (t, *J*=5.8 Hz, 1 H), 8.01 (d, *J*=1.4 Hz, 1 H), 7.93 (dd, *J*=8.2, 1.6 Hz, 1 H), 7.66 - 7.74 (m, 3 H), 7.60 - 7.65 (m, 1 H), 7.55 (ddd, *J*=7.9, 7.0, 1.4 Hz, 1 H), 7.20 (t, *J*=8.0 Hz, 1 H), 6.81 - 6.89 (m, 2 H), 6.78 (ddd, *J*=8.3, 2.4, 0.9 Hz, 1 H), 4.49 - 4.62 (m, *J*=13.9, 7.1, 7.1, 7.0 Hz, 1 H), 4.32 - 4.48 (m, 2 H), 3.71 - 3.80 (m, 1 H), 3.69 (s, 3 H), 1.18 (t, *J*=7.0 Hz, 3 H); LCMS RT = 5.26 min, *m*/*z* 435.1 [$M+H^+$]; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{23}N_2O_4S$ [$M+H^+$] 435.1373, found 435.1379.

EXAMPLE 9. 10-ETHYL-*N*-(2-METHOXYBENZYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 3)

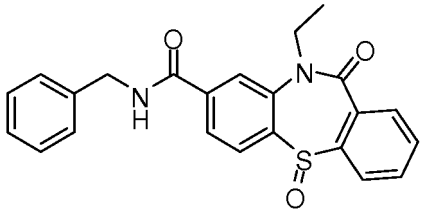
[0120]



[0121] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.97 (t, *J*=5.8 Hz, 1 H), 8.03 (d, *J*=1.6 Hz, 1 H), 7.94 (dd, *J*=8.2, 1.6 Hz, 1 H), 7.66 - 7.74 (m, 3 H), 7.60 - 7.66 (m, 1 H), 7.55 (ddd, *J*=7.9, 7.0, 1.4 Hz, 1 H), 7.18 - 7.25 (m, 1 H), 7.15 (dd, *J*=7.5, 1.7 Hz, 1 H), 6.93 - 6.99 (m, 1 H), 6.85 (td, *J*=7.4, 1.0 Hz, 1 H), 4.56 (dq, *J*=13.9, 7.1 Hz, 1 H), 4.31 - 4.48 (m, 2 H), 3.79 (s, 3 H), 3.71 - 3.78 (m, 1 H), 1.18 (t, *J*=7.0 Hz, 3 H); LCMS RT = 5.35 min, *m*/*z* 435.1 [M+H$^+$]; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{23}N_2O_4S$ [M+H$^+$] 435.1373, found 435.1373.

EXAMPLE 10. *N*-BENZYL-10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 4)

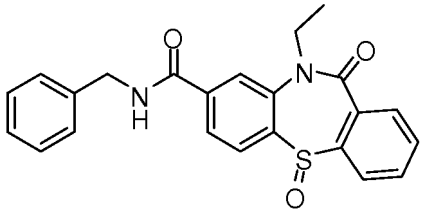
[0122]



[0123] The title compound was prepared according to the general protocol B. LCMS RT = 5.24 min, *m*/*z* 405.1 [M+H$^+$]; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{21}N_2O_3S$ [M+H$^+$] 405.1267, found 405.1268.

EXAMPLE 11. *N*-BENZYL-10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 4)

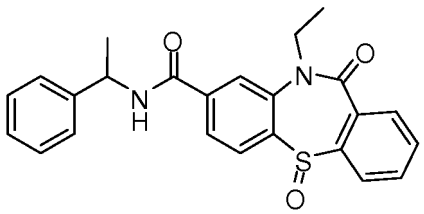
[0124]



[0125] Alternate procedure. The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.15 (t, *J*=5.9 Hz, 1 H), 8.02 (d, *J*=1.4 Hz, 1 H), 7.93 (dd, *J*=8.2, 1.6 Hz, 1 H), 7.65 - 7.73 (m, 3 H), 7.59 - 7.65 (m, 1 H), 7.55 (ddd, *J*=7.9, 6.9, 1.5 Hz, 1 H), 7.25 - 7.34 (m, 4 H), 7.16 - 7.25 (m, 1 H), 4.56 (sxt, *J*=6.9 Hz, 1 H), 4.34 - 4.51 (m, 2 H), 3.75 (sxt, *J*=7.0 Hz, 1 H), 1.18 (t, *J*=7.1 Hz, 3 H); LCMS RT = 5.23 min, *m*/*z* 405.1 [M+H$^+$]; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{21}N_2O_3S$ [M+H$^+$] 405.1267, found 405.1270.

EXAMPLE 12. 10-ETHYL-11-OXO-*N*-(1-PHENYLETHYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 5)

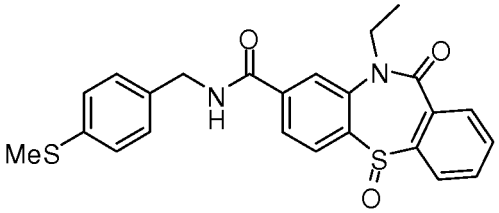
[0126]



[0127] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.91 (d, *J*=8.0 Hz, 0.5 H), 8.90 (d, *J*=8.0 Hz, 0.5 H), 8.00 (dd, *J*=7.2, 1.4 Hz, 1 H), 7.86 - 7.97 (m, 1 H), 7.60 - 7.77 (m, 4 H), 7.50 - 7.59 (m, 1 H), 7.24 - 7.39 (m, 4 H), 7.13 - 7.23 (m, 1 H), 5.10 (quin, *J*=7.5 Hz, 1 H), 4.44 - 4.72 (m, 1 H), 3.65 - 3.88 (m, 1 H), 1.44 (d, *J*=7.0 Hz, 1.5 H), 1.43 (d, *J*=7.0 Hz, 1.5 H), 1.18 (d, *J*=7.1 Hz, 1.5 H), 1.18 (d, *J*=7.1 Hz, 1.5 H); LCMS RT = 5.44 min, *m*/*z* 419.1 [M+H$^+$]; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{23}N_2O_3S$ [M+H$^+$] 419.1424, found 419.1428.

EXAMPLE 13. 10-ETHYL-*N*-(4-(METHYLTHIO)BENZYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 6)

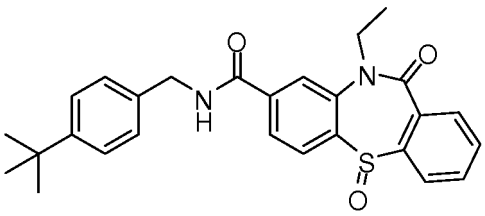
[0128]



[0129] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.12 (t, *J*=6.0 Hz, 1 H), 7.99 (d, *J*=1.4 Hz, 1 H), 7.91 (dd, *J*=8.2, 1.4 Hz, 1 H), 7.65 - 7.72 (m, 3 H), 7.59 - 7.65 (m, 1 H), 7.54 (td, *J*=7.3, 1.2 Hz, 1 H), 7.12 - 7.26 (m, 4 H), 4.55 (dq, *J*=14.1, 7.1 Hz, 1 H), 4.29 - 4.46 (m, 2 H), 3.73 (dq, *J*=13.9, 7.0 Hz, 1 H), 2.41 (s, 3 H), 1.17 (t, *J*=7.1 Hz, 3 H); LCMS RT = 5.58 min, *m*/*z* 451.1 [M+H$^+$]; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{23}N_2O_3S_2$ [M+H$^+$] 451.1145, found 451.1138.

EXAMPLE 14. *N*-(4-TERT-BUTYLBENZYL)-10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 7)

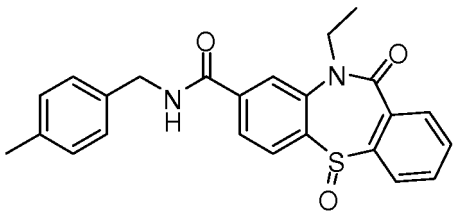
[0130]



[0131] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.09 (t, *J*=5.9 Hz, 1 H), 8.00 (d, *J*=1.4 Hz, 1 H), 7.91 (dd, *J*=8.1, 1.1 Hz, 1 H), 7.64 - 7.73 (m, 3 H), 7.60 - 7.64 (m, 1 H), 7.54 (td, *J*=7.4, 1.3 Hz, 1 H), 7.25 - 7.33 (m, 2 H), 7.19 (d, *J*=8.2 Hz, 2 H), 4.48 - 4.62 (m, 1 H), 4.31 - 4.46 (m, 2 H), 3.73 (dq, *J*=13.9, 6.9 Hz, 1 H), 1.22 (s, 9 H), 1.17 (t, *J*=7.1 Hz, 3 H); LCMS RT = 6.25 min, *m*/*z* 461.2 [M+H$^+$]; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{29}N_2O_3S$ [M+H$^+$] 461.1893, found 461.1889.

EXAMPLE 15. 10-ETHYL-*N*-(4-METHYLBENZYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 8)

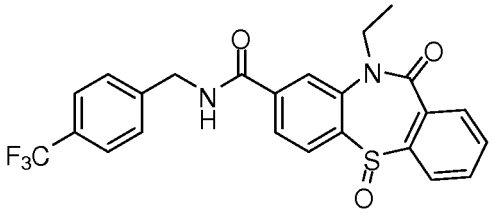
[0132]



[0133] The title compound was prepared according to the general protocol B. LCMS RT = 5.53 min, *m/z* 419.1 [M+H$^+$]; HRMS (ESI) *m/z* calcd for $C_{24}H_{23}N_2O_3S$ [M+H$^+$] 419.1424, found 419.1423.

EXAMPLE 16. 10-ETHYL-11-OXO-*N*-(4-(TRIFLUOROMETHYL)BENZYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 9)

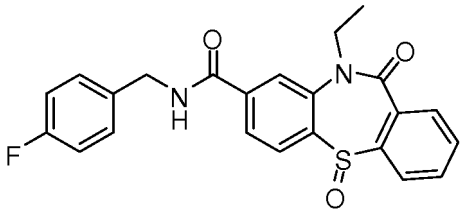
[0134]



[0135] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.25 (t, *J*=6.1 Hz, 1 H), 8.03 (d, *J*=1.6 Hz, 1 H), 7.94 (dd, *J*=8.2, 1.6 Hz, 1 H), 7.67 - 7.73 (m, 3 H), 7.61 - 7.67 (m, 3 H), 7.55 (ddd, *J*=7.9, 7.0, 1.5 Hz, 1 H), 7.50 (d, *J*=7.8 Hz, 2 H), 4.37 - 4.68 (m, 3 H), 3.63 - 3.86 (m, 1 H), 1.18 (t, *J*=7.1 Hz, 3 H); ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -60.84 (s, 3 F); LCMS RT = 5.81 min, *m/z* 473.1 [M+H$^+$]; HRMS (ESI) *m/z* calcd for $C_{24}H_{20}F_3N_2O_3S$ [M+H$^+$] 473.1141, found 473.1146.

EXAMPLE 17. 10-ETHYL-N-(4-FLUOROBENZYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 10)

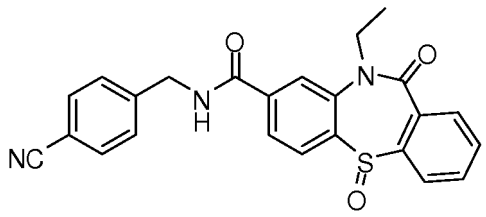
[0136]



[0137] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.15 (t, *J*=5.5 Hz, 1 H), 8.00 (d, *J*=1.4 Hz, 1 H), 7.91 (dd, *J*=8.1, 1.1 Hz, 1 H), 7.65 - 7.74 (m, 3 H), 7.59 - 7.65 (m, 1 H), 7.50 - 7.57 (m, 1 H), 7.25 - 7.35 (m, 2 H), 7.04 - 7.15 (m, 2 H), 4.55 (dq, *J*=14.0, 7.1 Hz, 1 H), 4.33 - 4.49 (m, 2 H), 3.73 (dq, *J*=13.8, 6.9 Hz, 1 H), 1.17 (t, *J*=7.0 Hz, 3 H); ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm - 116.20 - -116.06 (m, 1 F); LCMS RT = 5.34 min, *m/z* 423.1 [M+H$^+$]; HRMS (ESI) *m/z* calcd for $C_{23}H_{20}FN_2O_3S$ [M+H$^+$] 423.1173, found 423.1176.

EXAMPLE 18. N-(4-CYANOBENZYL)-10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 12)

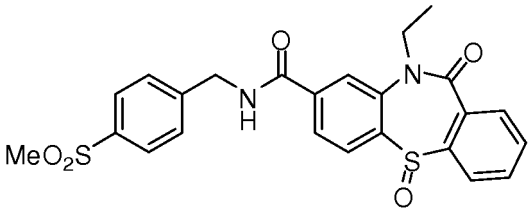
[0138]



[0139] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.15 (t, J=5.9 Hz, 1 H), 8.02 (d, J=1.4 Hz, 1 H), 7.93 (dd, J=8.2, 1.6 Hz, 1 H), 7.66 - 7.73 (m, 3 H), 7.61 - 7.65 (m, 1 H), 7.55 (ddd, J=7.9, 6.9, 1.5 Hz, 1 H), 7.25 - 7.32 (m, 3 H), 7.17 - 7.25 (m, 1 H), 4.51 - 4.61 (m, 1 H), 4.35 - 4.51 (m, 2 H), 3.75 (td, J=14.0, 7.3 Hz, 1 H), 1.18 (t, J=7.1 Hz, 3 H); LCMS RT = 5.05 min, m/z 452.1 [M+Na$^+$]; HRMS (ESI) m/z calcd for $C_{24}H_{20}N_3O_3S$ [M+H$^+$] 430.1220, found 430.1224.

EXAMPLE 19. 10-ETHYL-N-(4-(METHYLSULFONYL)BENZYL)-11-OXO-10,11-IHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 13)

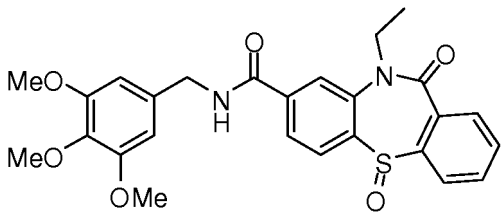
[0140]



[0141] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.27 (t, J=5.9 Hz, 1 H), 8.02 (d, J=1.2 Hz, 1 H), 7.93 (dd, J=8.3, 1.3 Hz, 1 H), 7.83 (d, J=8.0 Hz, 2 H), 7.66 - 7.74 (m, 3 H), 7.59 - 7.65 (m, 1 H), 7.49 - 7.58 (m, 3 H), 4.43 - 4.66 (m, 3 H), 3.74 (td, J=13.9, 6.8 Hz, 1 H), 3.14 (s, 3 H), 1.18 (t, J=7.0 Hz, 3 H); LCMS RT = 4.66 min, m/z 483.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{24}H_{23}N_2O_5S_2$ [M+H$^+$] 483.1043, found 483.1048.

EXAMPLE 20. 10-ETHYL-11-OXO-N-(3,4,5-TRIMETHOXYBENZYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 14)

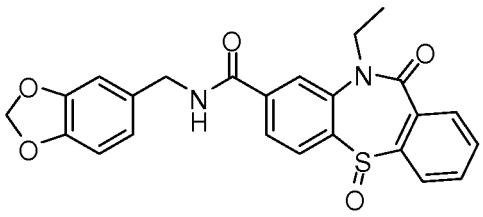
[0142]



[0143] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.06 (t, J=6.0 Hz, 1 H), 8.00 (d, J=1.6 Hz, 1 H), 7.92 (dd, J=8.2, 1.6 Hz, 1 H), 7.66 - 7.74 (m, 3 H), 7.61 - 7.65 (m, 1 H), 7.55 (ddd, J=7.9, 7.0, 1.4 Hz, 1 H), 6.61 (s, 2 H), 4.54 (dq, J=13.9, 7.2 Hz, 1 H), 4.30 - 4.45 (m, 2 H), 3.72 - 3.82 (m, 1 H), 3.71 (s, 6 H), 3.59 (s, 3 H), 1.18 (t, J=7.1 Hz, 3 H); LCMS RT = 5.01 min, m/z 495.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{26}H_{27}N_2O_6S$ [M+H$^+$] 495.1584, found 495.1589.

EXAMPLE 21. N-(BENZO[D][1,3]DIOXOL-5-YLMETHYL)-10-ETHYL-11-OXO-10,11 DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 15)

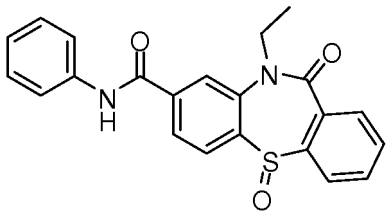
[0144]



[0145] The title compound was prepared according to the general protocol B. LCMS RT = 5.20 min, m/z 449.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{24}H_{21}N_2O_5S$ [M+H$^+$] 449.1166, found 449.1160.

EXAMPLE 22. 10-ETHYL-11-OXO-N-PHENYL-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 16)

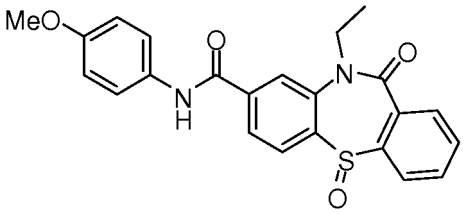
[0146]



[0147] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.31 (s, 1 H), 8.08 (d, J=1.6 Hz, 1 H), 7.96 (dd, J=8.0, 1.4 Hz, 1 H), 7.62 - 7.76 (m, 6 H), 7.56 (td, J=7.3, 1.4 Hz, 1 H), 7.33 (t, J=7.9 Hz, 2 H), 7.09 (t, J=7.4 Hz, 1 H), 4.59 (dq, J=13.9, 7.0 Hz, 1 H), 3.79 (td, J=13.9, 6.9 Hz, 1 H), 1.19 (t, J=7.0 Hz, 3 H); LCMS RT = 5.35 min, m/z 391.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{22}H_{19}N_2O_3S$ [M+H$^+$] 391.1111, found 391.1124.

EXAMPLE 23. 10-ETHYL-N-(4-METHOXYPHENYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 17)

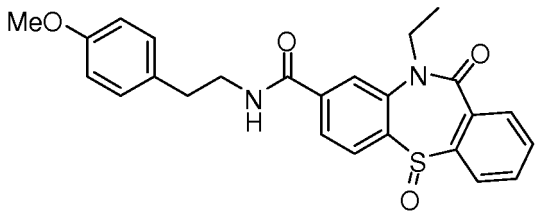
[0148]



[0149] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.20 (s, 1 H), 8.07 (d, J=1.4 Hz, 1 H), 7.96 (dd, J=8.2, 1.6 Hz, 1 H), 7.68 - 7.76 (m, 3 H), 7.62 - 7.67 (m, 1 H), 7.48 - 7.61 (m, 3 H), 6.85 - 6.95 (m, 2 H), 4.50 - 4.69 (m, 1 H), 3.74 - 3.85 (m, 1 H), 3.72 (s, 3 H), 1.20 (t, J=7.0 Hz, 3 H); LCMS RT = 5.27 min, m/z 421.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{23}H_{21}N_2O_4S$ [M+H$^+$] 421.1217, found 421.1215.

EXAMPLE 24. 10-ETHYL-N-(4-METHOXYPHENETHYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 18)

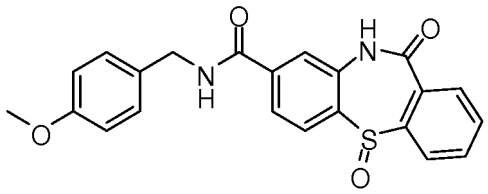
[0150]



[0151] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.65 (t, J=5.9 Hz, 1 H), 7.90 (d, J=1.4 Hz, 1 H), 7.84 (dd, J=8.2, 1.2 Hz, 1 H), 7.59 - 7.75 (m, 4 H), 7.54 (td, J=7.4, 1.3 Hz, 1 H), 7.07 - 7.14 (m, 2 H), 6.78 - 6.84 (m, 2 H), 4.54 (dq, J=14.1, 7.1 Hz, 1 H), 3.68 - 3.80 (m, 1 H), 3.68 (s, 3 H), 3.33 - 3.46 (m, 2 H), 2.71 (t, J=7.3 Hz, 2 H), 1.18 (t, J=7.1 Hz, 3 H); LCMS RT = 5.33 min, m/z 449.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{25}H_{25}N_2O_4S$ [M+H$^+$] 449.1530, found 449.1535.

EXAMPLE 25. N-(4-METHOXYBENZYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 19)

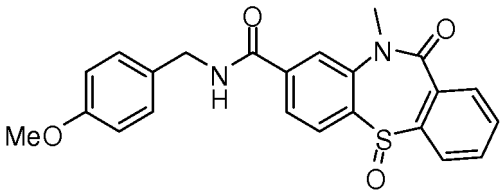
[0152]



[0153] The title compound was prepared according to the general protocol A. LCMS RT = 4.68 min, m/z 813.2 [2M+H$^+$]; HRMS (ESI) m/z calcd for $C_{22}H_{19}N_2O_4S$ [M+H$^+$] 407.1060, found 407.1056.

EXAMPLE 26. N-(4-METHOXYBENZYL)-10-METHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 20)

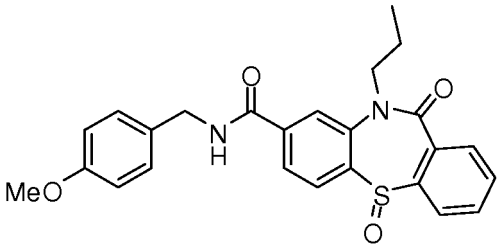
[0154]



[0155] The title compound was prepared according to the general protocol A. LCMS RT = 4.97 min, m/z 421.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{23}H_{21}N_2O_4S$ [M+H$^+$] 421.1217, found 421.1217.

EXAMPLE 27. N-(4-METHOXYBENZYL)-11-OXO-10-PROPYL-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 21)

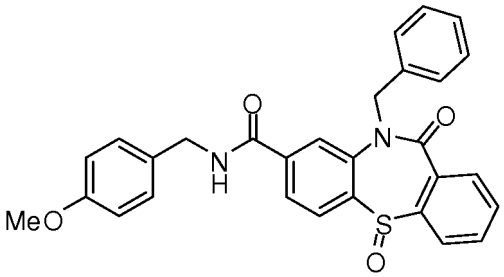
[0156]



[0157] The title compound was prepared according to the general protocol A. LCMS RT = 5.50 min, m/z 449.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{25}H_{25}N_2O_4S$ [M+H$^+$] 449.1530, found 449.1527.

EXAMPLE 28. 10-BENZYL-N-(4-METHOXYBENZYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 22)

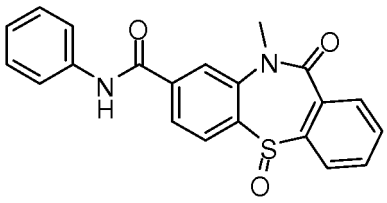
[0158]



[0159] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.05 (t, J=5.9 Hz, 1 H), 8.10 (d, J=1.4 Hz, 1 H), 7.84 (dd, J=8.2, 1.6 Hz, 1 H), 7.77 (dd, J=7.6, 1.0 Hz, 1 H), 7.67 - 7.74 (m, 1 H), 7.60 - 7.65 (m, 1 H), 7.54 - 7.60 (m, 2 H), 7.26 - 7.34 (m, 5 H), 7.15 - 7.23 (m, 2 H), 6.81 - 6.89 (m, 2 H), 5.77 (d, J=15.1 Hz, 1 H), 4.94 (d, J=15.1 Hz, 1 H), 4.27 - 4.48 (m, 2 H), 3.70 (s, 3 H); LCMS RT = 5.75 min, m/z 497.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{29}H_{25}N_2O_4S$ [M+H$^+$] 497.153, found 497.1526.

EXAMPLE 29. 10-METHYL-11-OXO-N-PHENYL-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 23)

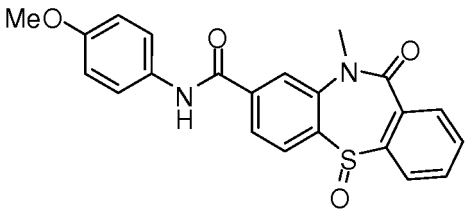
[0160]



[0161] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.31 (s, 1 H), 8.07 (d, J=1.4 Hz, 1 H), 7.96 (dd, J=8.1, 1.7 Hz, 1 H), 7.64 - 7.80 (m, 6 H), 7.58 (td, J=7.4, 1.4 Hz, 1 H), 7.20 - 7.42 (m, 2 H), 7.02 - 7.16 (m, 1 H), 3.59 (s, 3 H); LCMS RT = 5.18 min, m/z 377.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{21}H_{17}N_2O_3S$ [M+H$^+$] 377.0954, found 377.0953.

EXAMPLE 30. N-(4-METHOXYPHENYL)-10-METHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 24)

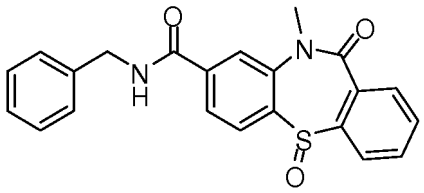
[0162]



[0163] The title compound was prepared according to the general protocol A. LCMS RT = 5.09 min, m/z 407.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{22}H_{19}N_2O_4S$ [M+H$^+$] 407.1060, found 407.1061.

EXAMPLE 31. N-BENZYL-10-METHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 25)

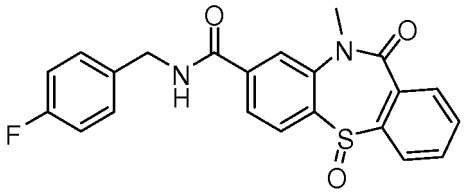
[0164]



[0165] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.15 (t, J=6.0 Hz, 1 H), 8.02 (s, 1 H), 7.93 (dt, J=8.2, 1.1 Hz, 1 H), 7.70 - 7.76 (m, 2 H), 7.64 - 7.69 (m, 2 H), 7.52 - 7.60 (m, 1 H), 7.25 - 7.33 (m, 4 H), 7.17 - 7.25 (m, 1 H), 4.35 - 4.53 (m, 2 H), 3.55 (d, J=1.0 Hz, 3 H); LCMS RT = 5.06 min, m/z 391.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{22}H_{19}N_2O_3S$ [M+H$^+$] 391.1111, found 391.1114.

EXAMPLE 32. N-(4-FLUOROBENZYL)-10-METHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 26)

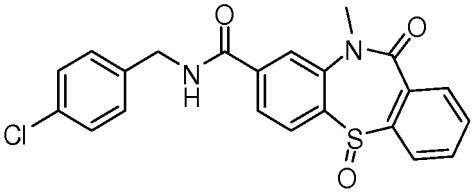
[0166]



[0167] The title compound was prepared according to the general protocol A. LCMS RT = 5.17 min, m/z 409.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{22}H_{18}FN_2O_3S$ [M+H$^+$] 409.1017, found 409.1019.

EXAMPLE 33. N-(4-CHLOROBENZYL)-10-METHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 27)

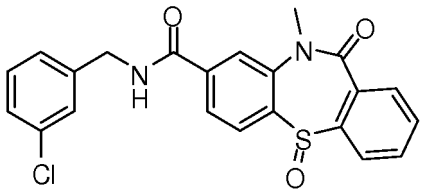
[0168]



[0169] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.18 (t, J=5.9 Hz, 1 H), 8.01 (d, J=1.4 Hz, 1 H), 7.92 (dd, J=8.2, 1.6 Hz, 1 H), 7.69 - 7.77 (m, 2 H), 7.62 - 7.69 (m, 2 H), 7.56 (ddd, J=8.0, 7.0, 1.5 Hz, 1 H), 7.26 - 7.40 (m, 4 H), 4.30 - 4.54 (m, 2 H), 3.54 (s, 3 H); LCMS RT = 5.48 min, m/z 425.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{22}H_{18}ClN_2O_3S$ [M+H$^+$] 425.0721, found 425.0724.

EXAMPLE 34. N-(3-CHLOROBENZYL)-10-METHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 28)

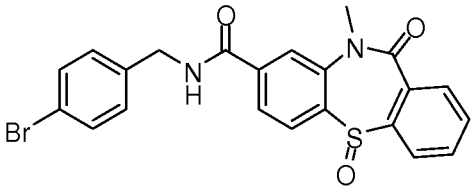
[0170]



[0171] The title compound was prepared according to the general protocol A. LCMS RT = 5.47 min, m/z 425.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{22}H_{18}ClN_2O_3S$ [M+H$^+$] 425.0721, found 425.0725.

EXAMPLE 35. N-(4-BROMOBENZYL)-10-METHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 29)

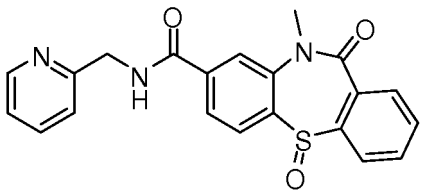
[0172]



[0173] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.18 (t, J=5.8 Hz, 1 H), 8.01 (d, J=1.4 Hz, 1 H), 7.92 (dd, J=8.2, 1.6 Hz, 1 H), 7.70 - 7.79 (m, 2 H), 7.62 - 7.70 (m, 2 H), 7.53 - 7.61 (m, 1 H), 7.41 - 7.52 (m, 2 H), 7.17 - 7.31 (m, 2 H), 4.30 - 4.49 (m, 2 H), 3.47 - 3.60 (m, 3 H); LCMS RT = 5.57 min, m/z 469.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{22}H_{18}BrN_2O_3S$ [M+H$^+$] 469.0216, found 469.0215.

EXAMPLE 36. 10-METHYL-11-OXO-N-(PYRIDIN-2-YLMETHYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 30)

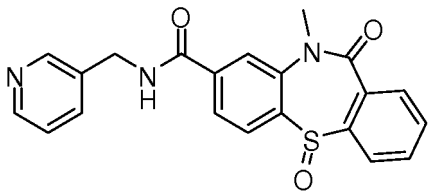
[0174]



[0175] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.17 - 9.39 (m, 1 H), 8.42 - 8.62 (m, 1 H), 8.05 (d, J=1.6 Hz, 1 H), 7.95 (dd, J=8.2, 1.6 Hz, 1 H), 7.77 - 7.90 (m, 1 H), 7.64 - 7.77 (m, 4 H), 7.57 (ddd, J=7.9, 7.0, 1.4 Hz, 1 H), 7.28 - 7.47 (m, 2 H), 4.52 - 4.65 (m, 2 H), 3.56 (s, 3 H); LCMS RT = 3.20 min, m/z 392.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{21}H_{18}N_3O_3S$ [M+H$^+$] 392.1063, found 392.1062.

EXAMPLE 37. 10-METHYL-11-OXO-N-(PYRIDIN-3-YLMETHYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 31)

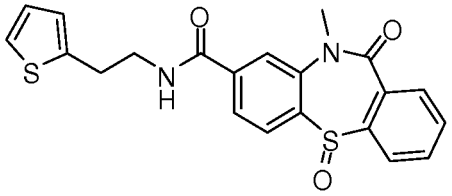
[0176]



[0177] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.34 (t, J=6.1 Hz, 1 H), 8.55 - 8.69 (m, 2 H), 8.05 (d, J=1.6 Hz, 1 H), 7.94 (dd, J=8.2, 1.6 Hz, 1 H), 7.65 - 7.78 (m, 4 H), 7.53 - 7.61 (m, 3 H), 4.53 - 4.63 (m, 2 H), 3.57 (s, 3 H); LCMS RT = 3.25 min, m/z 392.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{21}H_{18}N_3O_3S$ [M+H$^+$] 392.1063, found 392.1060.

EXAMPLE 38. 10-METHYL-11-OXO-N-(2-(THIOPHEN-2-YL)ETHYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 32, (Rac-55)

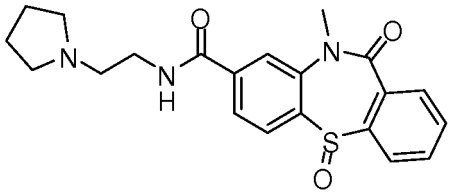
[0178]



[0179] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.76 (t, J=5.8 Hz, 1 H), 7.94 (d, J=1.6 Hz, 1 H), 7.86 (dd, J=8.2, 1.4 Hz, 1 H), 7.69 - 7.77 (m, 2 H), 7.67 (d, J=8.0 Hz, 2 H), 7.57 (td, J=7.4, 1.1 Hz, 1 H), 7.27 - 7.35 (m, 1 H), 6.83 - 6.98 (m, 2 H), 3.55 (s, 3 H), 3.40 - 3.51 (m, 2 H), 2.96 - 3.08 (m, 2 H); LCMS RT = 5.10 min, m/z 411.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_3S_2$ [M+H$^+$] 411.0832, found 411.0828.

EXAMPLE 39. 10-METHYL-11-OXO-N-(2-(PYRROLIDIN-1-YL)ETHYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 33)

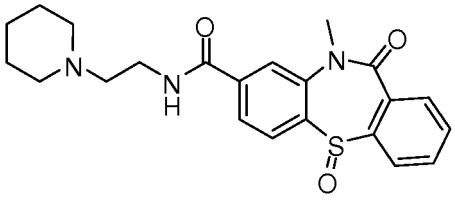
[0180]



[0181] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.68 - 8.93 (m, 1 H), 7.94 - 8.02 (m, 1 H), 7.84 - 7.94 (m, 1 H), 7.63 - 7.79 (m, 3 H), 7.51 - 7.63 (m, 1 H), 7.28 - 7.44 (m, 1 H), 3.56 (s, 3 H), 3.44 - 3.69 (m, 6 H), 3.03 (br. s., 2 H), 1.98 (br. s., 2 H), 1.71 - 1.89 (m, 2 H); LCMS RT = 3.27 min, m/z 398.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{21}H_{24}N_3O_3S$ [M+H$^+$] 398.1533, found 398.1538.

EXAMPLE 40. 10-METHYL-11-OXO-N-(2-(PIPERIDIN-1-YL)ETHYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 34)

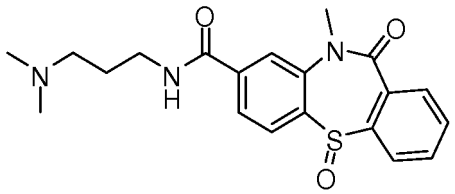
[0182]



[0183] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.82 (t, J=5.4 Hz, 1 H), 7.96 (d, J=1.6 Hz, 1 H), 7.89 (dd, J=8.2, 1.6 Hz, 1 H), 7.69 - 7.78 (m, 3 H), 7.64 - 7.69 (m, 1 H), 7.57 (td, J=7.5, 1.5 Hz, 1 H), 3.56 (s, 3 H), 3.53 - 3.67 (m, 2 H), 3.49 (d, J=12.7 Hz, 2 H), 3.14 - 3.23 (m, 2 H), 2.83 - 2.96 (m, 2 H), 1.80 (d, J=14.9 Hz, 2 H), 1.50 - 1.73 (m, 3 H), 1.28 - 1.43 (m, 1 H); LCMS RT = 3.39 min, m/z 412.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{22}H_{26}N_3O_3S$ [M+H$^+$] 412.1689, found 412.1694.

EXAMPLE 41. N-(3-(DIMETHYLAMINO)PROPYL)-10-METHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 35)

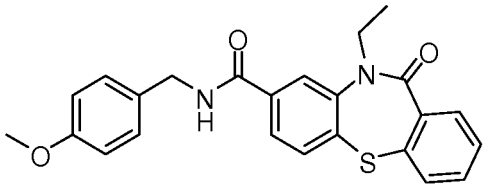
[0184]



[0185] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.72 (t, J=5.8 Hz, 1 H), 7.95 (d, J=1.4 Hz, 1 H), 7.88 (dd, J=8.2, 1.6 Hz, 1 H), 7.63 - 7.80 (m, 4 H), 7.57 (td, J=7.4, 1.4 Hz, 1 H), 3.56 (s, 3 H), 3.18 - 3.38 (m, 2 H), 2.97 - 3.11 (m, 2 H), 2.73 (s, 6 H), 1.71 - 1.92 (m, 2 H); LCMS RT = 3.21 min, m/z 386.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{20}H_{24}N_3O_3S$ [M+H$^+$] 386.1533, found 386.1535.

EXAMPLE 42. 10-ETHYL-N-(4-METHOXYBENZYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE (Compound 36)

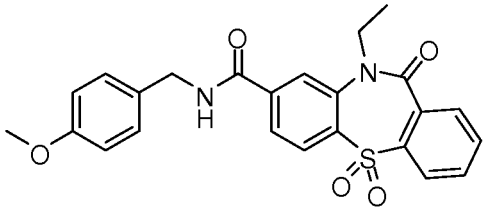
[0186]



[0187] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.03 (t, J=5.8 Hz, 1 H), 7.97 (d, J=1.6 Hz, 1 H), 7.69 - 7.78 (m, 1 H), 7.61 - 7.68 (m, 1 H), 7.54 - 7.60 (m, 1 H), 7.44 - 7.51 (m, 1 H), 7.32 - 7.42 (m, 2 H), 7.20 (d, J=8.2 Hz, 2 H), 6.85 (d, J=8.8 Hz, 2 H), 4.47 - 4.59 (m, 1 H), 4.25 - 4.44 (m, 2 H), 3.70 - 3.79 (m, 1 H), 3.69 (s, 3 H), 1.12 (t, J=7.0 Hz, 3 H); LCMS RT = 5.79 min, m/z 419.2 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{24}H_{23}N_2O_3S$ [M+H$^+$] 419.1424, found 419.1413.

EXAMPLE 43. N-(4-METHOXYBENZYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5,5-DIOXIDE (Compound 37)

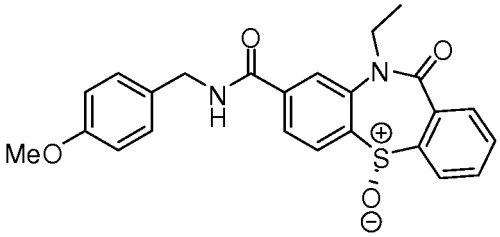
[0188]



[0189] A solution of 10-ethyl-N-(4-methoxybenzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide (10.0 mg, 0.024 mmol) in dichloromethane (3.00 mL) and was treated at room temperature with MCPBA (53.6 mg, 0.24 mmol). The reaction was stirred at room temperature for overnight. The reaction mixture was washed with saturated $Na_2S_2O_3$ solution. The organic layer was separated, dried and concentrated. The crude mixture was purified by preparative HPLC to give 2.0 mg (19%) of the title compound as a white foam. LCMS RT = 5.46 min, m/z 451.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{24}H_{23}N_2O_5S$ [M+H$^+$] 451.1322, found 451.1322.

EXAMPLE 44. 10-ETHYL-N-(4-METHOXYBENZYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-(S)-OXIDE (Compound 38)

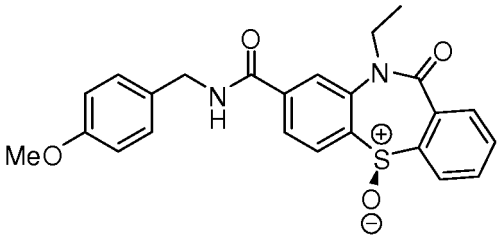
[0190]



[0191] LCMS RT = 5.22 min, m/z 435.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{24}H_{23}N_2O_4S$ [M+H$^+$] 435.1373, found 435.1353.

EXAMPLE 45. 10-ETHYL-N-(4-METHOXYBENZYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-(R)-OXIDE (Compound 39)

[0192]

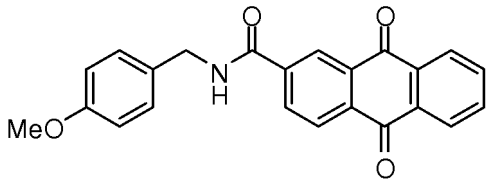


[0193] Separation of enantiomers via chiral HPLC: Analytical analysis was performed on a CHIRALPAK®IA® column (4.6 × 150 mm, 5 micron). The mobile phase was 60% of isopropanol in hexanes at a flow rate of 1.0 mL/min with a run time of 15 minutes. The sample was detected with a diode array detector (DAD) at 220 nm and 254 nm. Optical rotation was determined with an in-line polarimeter (PDR-Chiral). The first eluting peak: RT = 5.22 minutes; positive optical rotation. The second eluting peak: RT = 5.61 minutes; negative optical rotation. Preparative separation was performed on a CHIRALPAK®IA® column (5× 50 cm, 20 micron). The mobile phase was 60% of isopropanol in hexanes at a flow rate of 30 mL/min. Fraction collection was triggered by UV absorbance (254 nm). LCMS RT = 5.22 min, m/z

435.1 [M+H+]; HRMS (ESI) m/z calcd for $C_{24}H_{23}N_2O_4S$ [M+H+] 435.1373, found 435.1356.

EXAMPLE 46. N-(4-METHOXYBENZYL)-9,10-DIOXO-9,10-DIHYDROANTHRACENE-2-CARBOXAMIDE (Compound 40)

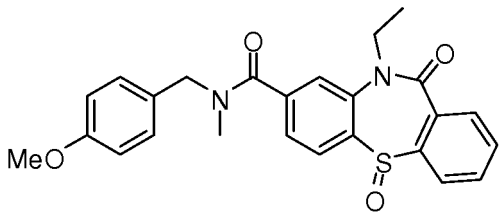
[0194]



[0195] A solution of 9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid (1.00 g, 3.96 mmol) in DMF (15.0 mL) was treated at room temperature with (4-methoxyphenyl)methanamine (1.09 g, 7.93 mmol), HATU (2.26 g, 5.95 mmol) and DIPEA (2.08 mL, 11.9 mmol). The reaction mixture was stirred at room temperature for 2 hours. The mixture was concentrated and purified by Biotage with 0-20% of MeOH in CH_2Cl_2 to give 1.30 g (88%) of the title compound as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.45 (t, J=5.3 Hz, 1 H), 8.67 (t, J=1.8 Hz, 1 H), 8.33 - 8.39 (m, 1 H), 8.18 - 8.31 (m, 3 H), 7.95 (ddd, J=5.6, 3.4, 2.2 Hz, 2 H), 7.20 - 7.32 (m, 2 H), 6.80 - 6.97 (m, 2 H), 4.45 (d, J=5.7 Hz, 2 H), 3.72 (s, 3 H); LCMS RT = 5.99 min, m/z 372.0 [M+H+].

EXAMPLE 47. 10-ETHYL-N-(4-METHOXYBENZYL)-N-METHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 42)

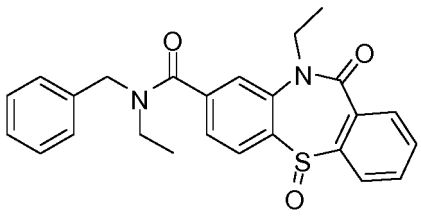
[0196]



[0197] A solution of 10-ethyl-N-(4-methoxybenzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide in DMF (2.50 mL) was treated at 0 °C with NaH (18.4 mg, 0.46 mmol). The reaction mixture was warmed to room temperature and stirred at room temperature for 1 h. a solution of MeI (0.029 mL, 0.46 mmol) in DMF (1.00 mL) was added to the mixture dropwisely. The reaction mixture was stirred at room temperature for 1.5 h. Water was carefully added and the aqueous layer was extracted with 20% MeOH in dichloromethane. The aqueous layer was separated, dried, concentrated and purified by preparative HPLC to give 12.0 mg (58%) of the title compound. LCMS RT = 5.26 min, m/z 449.1 [M+H+]; HRMS (ESI) m/z calcd for $C_{21}H_{16}NO_4S$ [M+H+] 449.1530, found 449.1524.

EXAMPLE 48. N-BENZYL-N,10-DIETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE (Compound 43)

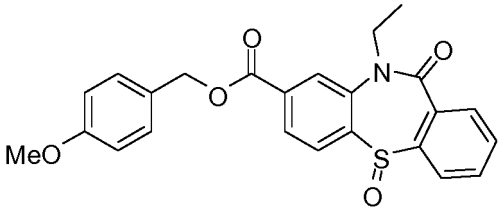
[0198]



[0199] The title compound was prepared according to the general protocol A. LCMS RT = 5.54 min, m/z 433.1 [M+H+]; HRMS (ESI) m/z calcd for $C_{25}H_{25}N_2O_3S$ [M+H+] 433.1580, found 433.1580.

EXAMPLE 49. 10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-(4-METHOXYBENZYL)CARBOXYLATE 5-OXIDE (Compound 44)

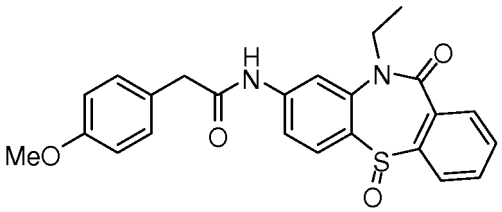
[0200]



[0201] A solution of 10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxylic acid 5-oxide (180 mg, 0.57 mmol) in DMF (5.00 mL) and was treated at 0 °C with NaH (68.5 mg, 1.71 mmol). The reaction mixture was warmed to room temperature and stirred at room temperature for 1 h. A solution of 1-(bromomethyl)-4-methoxybenzene (344 mg, 1.71 mmol) in DMF (2.00 mL) was added dropwisely to the mixture. The reaction mixture was stirred at room temperature for 1.5 h. Water was carefully added and the aqueous layer was extracted with EtOAc. The organic layer was separated, dried, concentrated and purified by preparative HPLC to give 21.6 mg (9%) of the title compound. The title compound also can be prepared using a different protocol: A solution of 10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxylic acid 5-oxide (50.0 mg, 0.16 mmol) in DMF (2.00 mL) was treated at room temperature with K_2CO_3 (110 mg, 0.79 mmol) and 1-(bromomethyl)-4-methoxybenzene (96 mg, 0.48 mmol). The reaction mixture was stirred at room temperature for overnight. The reaction mixture was filtered and purified by preparative HPLC to give 7.2 mg (10%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.07 (d, J=1.4 Hz, 1 H), 8.00 (dd, J=8.1, 1.5 Hz, 1 H), 7.74 (d, J=8.2 Hz, 1 H), 7.66 - 7.71 (m, 2 H), 7.60 - 7.65 (m, 1 H), 7.51 - 7.59 (m, 1 H), 7.31 - 7.40 (m, 2 H), 6.83 - 6.96 (m, 2 H), 5.25 (q, J=11.9 Hz, 2 H), 4.55 (dq, J=14.0, 7.1 Hz, 1 H), 3.73 (s, 3 H), 3.62 - 3.78 (m, 1 H), 1.16 (t, J=7.1 Hz, 3 H); LCMS RT = 6.12 min, m/z 458.1 [M+Na$^+$]; HRMS (ESI) m/z calcd for $C_{24}H_{21}NNaO_5S$ [M+Na$^+$] 458.1033, found 458.1029.

EXAMPLE 50. N-(10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPIN-8-YL)-2-(4-METHOXYPHENYL)ACETAMIDE 5-OXIDE (Compound 45)

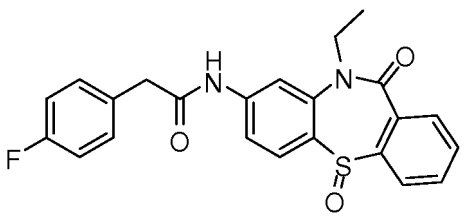
[0202]



[0203] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.44 (s, 1 H), 7.93 (d, J=1.6 Hz, 1 H), 7.64 - 7.73 (m, 2 H), 7.46 - 7.63 (m, 4 H), 7.12 - 7.23 (m, 2 H), 6.76 - 6.89 (m, 2 H), 4.28 - 4.53 (m, 1 H), 3.69 (s, 3 H), 3.58 - 3.73 (m, 1 H), 3.54 (s, 2 H), 1.21 (t, J=7.0 Hz, 3 H); LCMS RT = 5.39 min, m/z 435.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{24}H_{23}N_2O_4S$ [M+H$^+$] 435.1373, found 435.1371.

EXAMPLE 51. N-(10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPIN-8-YL)-2-(4-FLUOROPHENYL)ACETAMIDE 5-OXIDE (Compound 46)

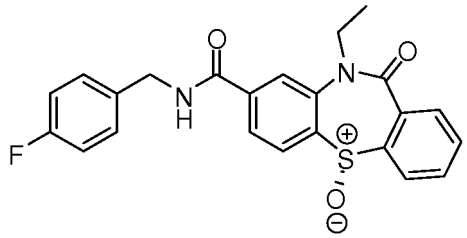
[0204]



[0205] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.49 (s, 1 H), 7.93 (d, J=2.0 Hz, 1 H), 7.64 - 7.73 (m, 2 H), 7.47 - 7.64 (m, 4 H), 7.24 - 7.39 (m, 2 H), 7.01 - 7.19 (m, 2 H), 4.40 (dq, J=13.8, 7.2 Hz, 1 H), 3.62 (s, 2 H), 3.55 - 3.71 (m, 1 H), 1.21 (t, J=7.0 Hz, 3 H); ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -116.73 - -116.14 (m, 1 F); LCMS RT = 5.50 min, m/z 423.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{23}H_{20}FN_2O_3S$ [M+H$^+$] 423.1173, found 423.1174.

EXAMPLE 52. 10-ETHYL-N-(4-FLUOROBENZYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-(S)-OXIDE (Compound 47)

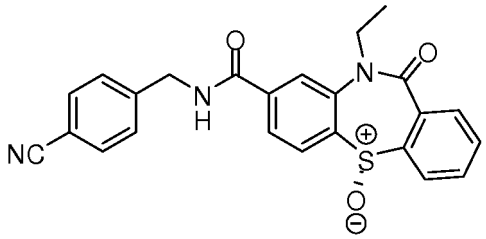
[0206]



[0207] LCMS RT = 5.43 min, m/z 423.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{23}H_{20}FN_2O_3S$ [M+H$^+$] 423.1173, found 423.1181.

EXAMPLE 53. N-(4-CYANOBENZYL)-10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-(S)-OXIDE (Compound 48)

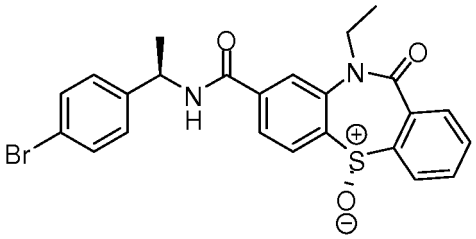
[0208]



[0209] LCMS RT = 5.14 min, m/z 430.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{24}H_{20}N_3O_3S$ [M+H$^+$] 430.1220, found 430.1223.

EXAMPLE 54. (R)-N-(1-(4-BROMOPHENYL)ETHYL)-10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-(S)-OXIDE (Compound 49)

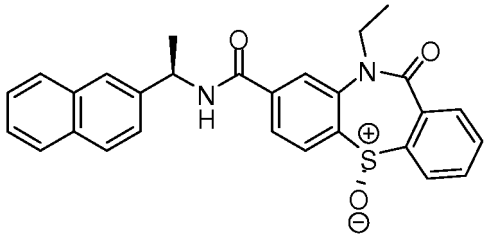
[0210]



[0211] LCMS RT = 6.02 min, m/z 497.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{24}H_{22}BrN_2O_3S$ [M+H$^+$] 497.0529, found 497.0528.

EXAMPLE 55. (R)-10-ETHYL-N-(1-(NAPHTHALEN-2-YL)ETHYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-(S)-OXIDE (Compound 50)

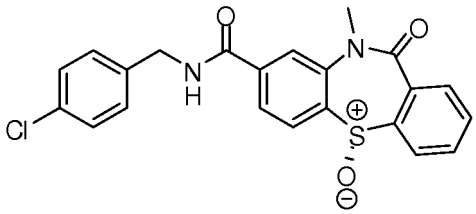
[0212]



[0213] LCMS RT = 6.07 min, m/z 469.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{28}H_{25}N_2O_3S$ [M+H$^+$] 469.1580, found 469.1586.

EXAMPLE 56. N-(4-CHLOROBENZYL)-10-METHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-(S)-OXIDE (Compound 51)

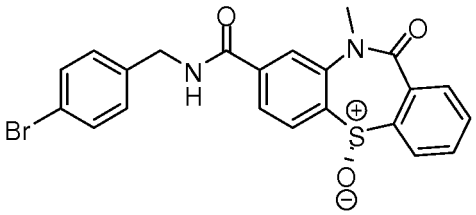
[0214]



[0215] LCMS RT = 5.47 min, m/z 425.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{22}H_{18}ClN_2O_3S$ [M+H$^+$] 425.0721, found 425.0726.

EXAMPLE 57. N-(4-BROMOBENZYL)-10-METHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-(S)-OXIDE (Compound 52)

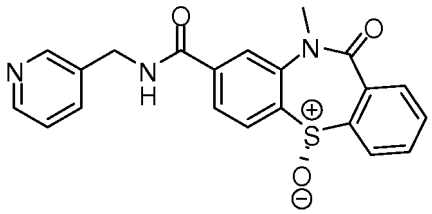
[0216]



[0217] LCMS RT = 5.57 min, m/z 469.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{22}H_{18}BrN_2O_3S$ [M+H$^+$] 469.0216, found 469.0215.

EXAMPLE 58. 10-METHYL-11-OXO-N-(PYRIDIN-3-YLMETHYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-(S)-OXIDE (Compound 53)

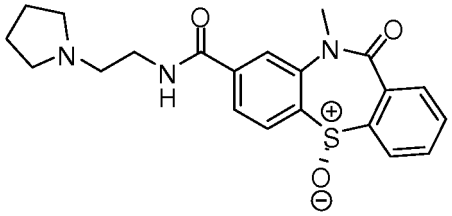
[0218]



[0219] LCMS RT = 3.35 min, m/z 392.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{21}H_{18}N_3O_3S$ [M+H$^+$] 392.1063, found 392.1067.

EXAMPLE 59. 10-METHYL-11-OXO-N-(2-(PYRROLIDIN-1-YL)ETHYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-(S)-OXIDE (Compound 54)

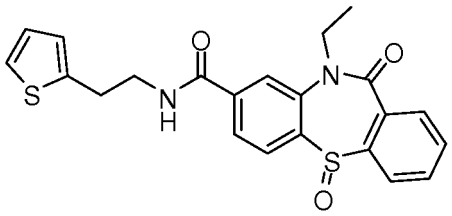
[0220]



[0221] LCMS RT = 3.36 min, m/z 398.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{21}H_{24}N_3O_3S$ [M+H$^+$] 398.1533, found 398.1537.

EXAMPLE 60. 10-ETHYL-11-OXO-N-(2-(THIOPHEN-2-YL)ETHYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

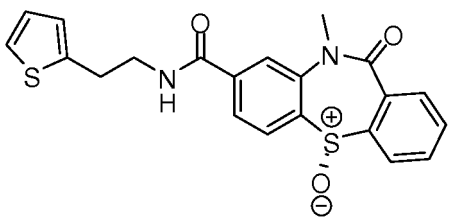
[0222]



[0223] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.76 (t, J=6.1 Hz, 1 H), 7.93 (d, J=1.4 Hz, 1 H), 7.86 (dd, J=8.1, 0.9 Hz, 1 H), 7.60 - 7.72 (m, 4 H), 7.50 - 7.57 (m, 1 H), 7.30 (dd, J=5.8, 1.1 Hz, 1 H), 6.91 (dd, J=5.1, 3.3 Hz, 1 H), 6.87 (d, J=3.5 Hz, 1 H), 4.47 - 4.61 (m, 1 H), 3.73 (td, J=13.8, 6.8 Hz, 1 H), 3.39 - 3.51 (m, 2 H), 3.01 (t, J=7.1 Hz, 2 H), 1.18 (t, J=7.1 Hz, 3 H); LCMS RT = 5.27 min, m/z 425.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{22}H_{21}N_2O_3S_2$ [M+H$^+$] 425.0988, found 425.0988.

EXAMPLE 61. 10-METHYL-11-OXO-N-(2-(THIOPHEN-2-YL)ETHYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-(S)-OXIDE (Compound 55)

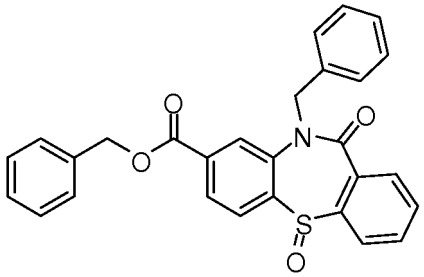
[0224]



[0225] LCMS RT = 5.08 min, m/z 411.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_3S_2$ [M+H$^+$] 411.0832, found 411.0831.

EXAMPLE 62. BENZYL 10-BENZYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXYLATE 5-OXIDE

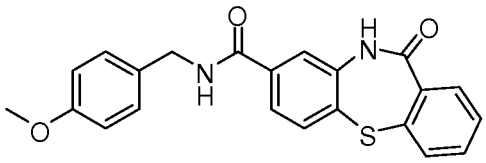
[0226]



[0227] A suspension of benzyl 10-benzyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxylate (30.0 mg, 0.066 mmol) in acetic acid (3.00 mL) was treated at room temperature with H_2O_2 (0.17 mL, 1.66 mmol). The reaction mixture was stirred at room temperature for overnight. The mixture was poured into ice water and the precipitation was filtered, washed and dried to the title compound 21.0 mg (68%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.13 (d, J=1.6 Hz, 1 H), 7.95 (dd, J=8.2, 1.6 Hz, 1 H), 7.53 - 7.81 (m, 5 H), 7.24 - 7.43 (m, 9 H), 7.16 - 7.24 (m, 1 H), 5.64 (d, J=15.3 Hz, 1 H), 5.30 (s, 2 H), 5.03 (d, J=15.3 Hz, 1 H); LCMS RT = 6.61 min, m/z 468.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{28}H_{22}NO_4S$ [M+H$^+$] 468.1264, found 468.1263.

EXAMPLE 63. N-(4-METHOXYBENZYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE

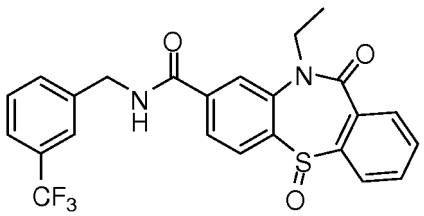
[0228]



[0229] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.74 (s, 1 H), 8.98 (t, J=5.7 Hz, 1 H), 7.55 - 7.72 (m, 4 H), 7.37 - 7.54 (m, 3 H), 7.13 - 7.22 (m, 2 H), 6.79 - 6.87 (m, 2 H), 4.33 (d, J=5.9 Hz, 2 H), 3.68 (s, 3 H); LCMS RT = 5.31 min, m/z 391.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{22}H_{19}N_2O_3S$ [M+H$^+$] 391.1111, found 391.1098.

EXAMPLE 64. 10-ETHYL-11-OXO-N-(3-(TRIFLUOROMETHYL)BENZYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

[0230]

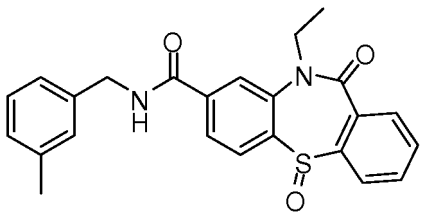


[0231] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (t, J=6.1 Hz, 1 H), 8.02 (d, J=1.4 Hz, 1 H), 7.93 (dd, J=8.0, 1.6 Hz, 1 H), 7.66 - 7.74 (m, 3 H), 7.49 - 7.66 (m, 6 H),

4.43 - 4.65 (m, 3 H), 3.74 (dq, J=13.8, 7.0 Hz, 1 H), 1.18 (t, J=7.1 Hz, 3 H); ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -61.04 (s, 3 F); LCMS RT = 5.78 min, m/z 473.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{24}H_{20}F_3N_2O_3S$ [M+H$^+$] 473.1141, found 473.1146.

EXAMPLE 65. 10-ETHYL-N-(3-METHYLBENZYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

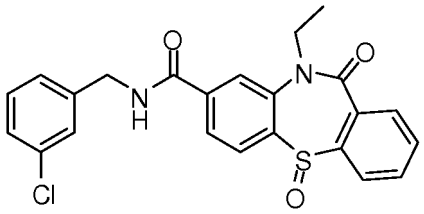
[0232]



[0233] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.12 (t, J=6.0 Hz, 1 H), 8.01 (d, J=1.4 Hz, 1 H), 7.93 (dd, J=8.0, 1.6 Hz, 1 H), 7.66 - 7.74 (m, 3 H), 7.61 - 7.65 (m, 1 H), 7.55 (ddd, J=7.9, 7.0, 1.4 Hz, 1 H), 7.17 (t, J=7.5 Hz, 1 H), 6.98 - 7.12 (m, 3 H), 4.50 - 4.62 (m, 1 H), 4.32 - 4.48 (m, 2 H), 3.75 (dq, J=13.9, 7.0 Hz, 1 H), 2.25 (s, 3 H), 1.18 (t, J=7.1 Hz, 3 H); LCMS RT = 5.54 min, m/z 419.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{24}H_{23}N_2O_3S$ [M+H$^+$] 419.1424, found 419.1427.

EXAMPLE 66. N-(3-CHLOROBENZYL)-10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

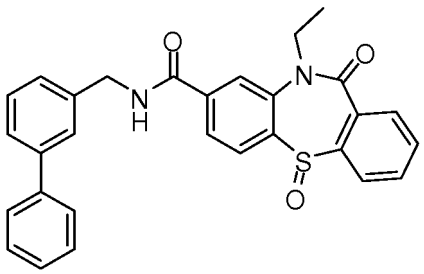
[0234]



[0235] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.18 (t, J=6.0 Hz, 1 H), 8.02 (d, J=1.4 Hz, 1 H), 7.93 (dd, J=8.2, 1.6 Hz, 1 H), 7.66 - 7.74 (m, 3 H), 7.61 - 7.66 (m, 1 H), 7.55 (td, J=7.4, 1.4 Hz, 1 H), 7.22 - 7.37 (m, 4 H), 4.51 - 4.62 (m, 1 H), 4.37 - 4.51 (m, 2 H), 3.75 (dq, J=13.9, 7.0 Hz, 1 H), 1.18 (t, J=7.1 Hz, 3 H); LCMS RT = 5.64 min, m/z 439.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{23}H_{20}ClN_2O_3S$ [M+H$^+$] 439.0878, found 439.0882.

EXAMPLE 67. N-(BIPHENYL-3-YLMETHYL)-10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

[0236]

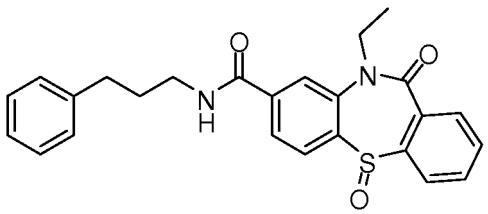


[0237] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm

9.18 (t, J=5.9 Hz, 1 H), 8.03 (d, J=1.4 Hz, 1 H), 7.94 (dd, J=8.2, 1.6 Hz, 1 H), 7.25 - 7.76 (m, 14 H), 4.37 - 4.70 (m, 3 H), 3.75 (dd, J=13.8, 6.9 Hz, 1 H), 1.18 (t, J=7.0 Hz, 3 H); LCMS RT = 6.10 min, m/z 481.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{29}H_{25}N_2O_3S$ [M+H$^+$] 481.1580, found 481.1581.

EXAMPLE 68. 10-ETHYL-11-OXO-N-(3-PHENYLPROPYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

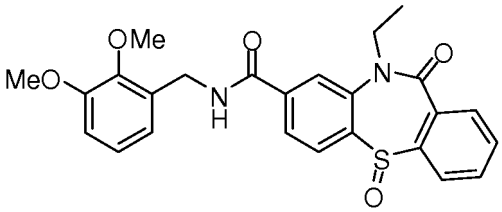
[0238]



[0239] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.58 (t, J=5.8 Hz, 1 H), 7.93 (d, J=1.4 Hz, 1 H), 7.87 (dd, J=8.2, 1.6 Hz, 1 H), 7.64 - 7.73 (m, 3 H), 7.61 - 7.64 (m, 1 H), 7.55 (ddd, J=7.9, 7.0, 1.4 Hz, 1 H), 7.21 - 7.28 (m, 2 H), 7.10 - 7.21 (m, 3 H), 4.48 - 4.62 (m, 1 H), 3.67 - 3.82 (m, 1 H), 3.15 - 3.28 (m, 2 H), 2.55 - 2.62 (m, 2 H), 1.78 (ddd, J=14.9, 7.4, 7.2 Hz, 2 H), 1.18 (t, J=7.0 Hz, 3 H); LCMS RT = 5.65 min, m/z 433.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{25}H_{25}N_2O_3S$ [M+H$^+$] 433.1580, found 433.1586.

EXAMPLE 69. N-(2,3-DIMETHOXYBENZYL)-10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

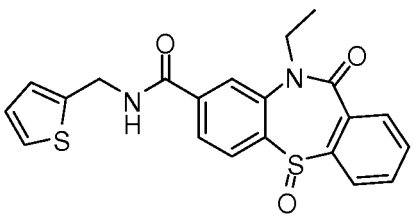
[0240]



[0241] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.01 (t, J=5.9 Hz, 1 H), 8.01 (d, J=1.4 Hz, 1 H), 7.93 (dd, J=8.2, 1.6 Hz, 1 H), 7.66 - 7.74 (m, 3 H), 7.60 - 7.65 (m, 1 H), 7.55 (ddd, J=7.9, 7.0, 1.4 Hz, 1 H), 6.86 - 7.02 (m, 2 H), 6.81 (dd, J=7.6, 1.8 Hz, 1 H), 4.50 - 4.62 (m, 1 H), 4.37 - 4.50 (m, 2 H), 3.77 (s, 3 H), 3.72 (s, 3 H), 3.68 - 3.80 (m, 1 H), 1.18 (t, J=7.1 Hz, 3 H); LCMS RT = 5.26 min, m/z 465.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{25}H_{25}N_2O_5S$ [M+H$^+$] 465.1479, found 465.1481.

EXAMPLE 70. 10-ETHYL-11-OXO-N-(THIOPHEN-2-YLMETHYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

[0242]

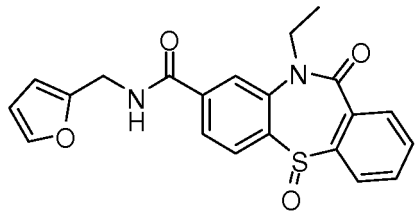


[0243] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.25 (t, J=6.0 Hz, 1 H), 7.98 (d, J=1.6 Hz, 1 H), 7.90 (dd, J=8.0, 1.4 Hz, 1 H), 7.66 - 7.73 (m, 3 H), 7.59 - 7.64 (m, 1 H), 7.54 (td, J=7.3, 1.3 Hz, 1 H), 7.35 (dd, J=4.5, 1.2 Hz, 1 H), 6.99 (d, J=4.1 Hz, 1 H), 6.92 (dd, J=5.1, 3.3 Hz, 1 H), 4.46

- 4.70 (m, 3 H), 3.65 - 3.79 (m, 1 H), 1.17 (t, J=7.1 Hz, 3 H); LCMS RT = 5.13 min, m/z 411.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_3S_2$ [M+H$^+$] 411.0832, found 411.0828.

EXAMPLE 71. 10-ETHYL-N-(FURAN-2-YLMETHYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

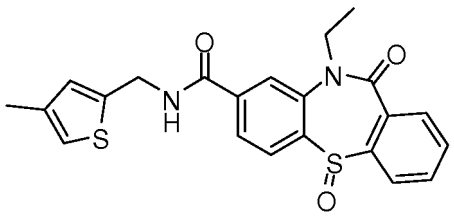
[0244]



[0245] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.09 (t, J=5.7 Hz, 1 H), 7.99 (d, J=1.6 Hz, 1 H), 7.90 (dd, J=8.2, 1.6 Hz, 1 H), 7.65 - 7.72 (m, 3 H), 7.61 - 7.64 (m, 1 H), 7.51 - 7.57 (m, 2 H), 6.36 (dd, J=3.1, 1.8 Hz, 1 H), 6.27 (dd, J=3.1, 0.8 Hz, 1 H), 4.56 (dq, J=13.9, 7.0 Hz, 1 H), 4.36 - 4.49 (m, 2 H), 3.74 (dq, J=13.9, 7.0 Hz, 1 H), 1.17 (t, J=7.1 Hz, 3 H); LCMS RT = 4.92 min, m/z 395.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_4S$ [M+H$^+$] 395.1060, found 395.1071.

EXAMPLE 72. 10-ETHYL-N-((4-METHYLTHIOPHEN-2-YL)METHYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

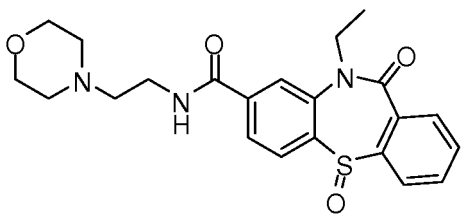
[0246]



[0247] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.21 (t, J=6.0 Hz, 1 H), 7.98 (d, J=1.6 Hz, 1 H), 7.90 (dd, J=8.2, 1.6 Hz, 1 H), 7.66 - 7.73 (m, 3 H), 7.61 - 7.65 (m, 1 H), 7.54 (ddd, J=7.9, 7.0, 1.4 Hz, 1 H), 6.88 - 6.94 (m, 1 H), 6.80 (d, J=1.0 Hz, 1 H), 4.42 - 4.69 (m, 3 H), 3.65 - 3.85 (dq, J=13.8, 7.1 Hz, 1 H), 2.12 (d, J=1.0 Hz, 3 H), 1.18 (t, J=7.1 Hz, 3 H); LCMS RT = 5.44 min, m/z 425.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{22}H_{21}N_2O_3S_2$ [M+H$^+$] 425.0988, found 425.0993.

EXAMPLE 73. 10-ETHYL-N-(2-MORPHOLINOETHYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

[0248]

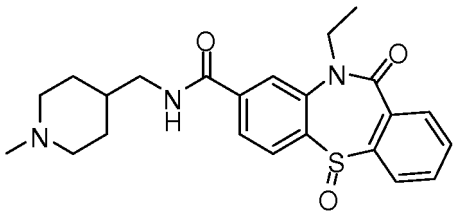


[0249] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.40 (br. s., 1 H), 8.83 (br. s., 1 H), 7.97 (d, J=1.4 Hz, 1 H), 7.90 (dd, J=8.3, 1.1 Hz, 1 H), 7.67 - 7.76 (m, 2 H), 7.61 - 7.66 (m, 1 H), 7.55 (ddd, J=7.9, 6.9, 1.4 Hz, 1 H), 4.58 (td, J=14.1, 7.2 Hz, 2 H), 3.97 (d, J=12.3 Hz, 2 H), 3.72 (td, J=13.8, 6.9 Hz, 2 H), 3.59 (t, J=12.1 Hz, 4 H), 3.49 (d, J=11.2 Hz, 2 H), 3.03 - 3.18 (m, 2 H), 1.19 (t, J=7.1 Hz, 3 H);

LCMS RT = 3.48 min, m/z 428.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{22}H_{26}N_3O_4S$ [M+H$^+$] 428.1639, found 428.1644.

EXAMPLE 74. 10-ETHYL-N-((1-METHYLPIPERIDIN-4-YL)METHYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

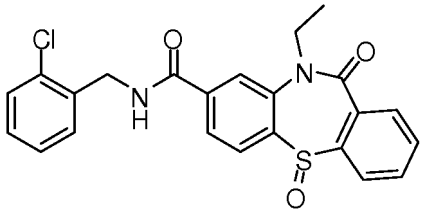
[0250]



[0251] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.96 (br. s., 1 H), 8.67 (t, J=5.3 Hz, 1 H), 7.95 (d, J=1.6 Hz, 1 H), 7.88 (dd, J=8.2, 1.6 Hz, 1 H), 7.66 - 7.73 (m, 2 H), 7.60 - 7.66 (m, 1 H), 7.55 (ddd, J=7.9, 7.0, 1.4 Hz, 1 H), 4.58 (td, J=13.8, 6.7 Hz, 1 H), 3.73 (td, J=13.9, 6.8 Hz, 1 H), 3.34 - 3.43 (m, 2 H), 3.19 (ddd, J=12.8, 6.7, 6.5 Hz, 1 H), 3.09 (ddd, J=13.1, 6.5, 6.3 Hz, 1 H), 2.78 - 2.90 (m, 2 H), 2.71 (d, J=4.9 Hz, 3 H), 1.78 - 1.90 (m, 2 H), 1.70 (br. s., 1 H), 1.23 - 1.37 (m, 2 H), 1.18 (t, J=7.1 Hz, 3 H); LCMS RT = 3.54 min, m/z 426.2 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{23}H_{28}N_3O_3S$ [M+H$^+$] 426.1846, found 426.1846.

EXAMPLE 75. N-(2-CHLOROBENZYL)-10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

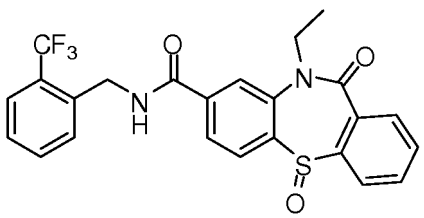
[0252]



[0253] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.16 (t, J=5.8 Hz, 1 H), 8.04 (d, J=1.6 Hz, 1 H), 7.95 (dd, J=8.2, 1.6 Hz, 1 H), 7.66 - 7.75 (m, 3 H), 7.61 - 7.66 (m, 1 H), 7.55 (ddd, J=7.9, 6.9, 1.5 Hz, 1 H), 7.38 - 7.46 (m, 1 H), 7.31 - 7.38 (m, 1 H), 7.23 - 7.31 (m, 2 H), 4.42 - 4.66 (m, 3 H), 3.76 (dq, J=13.8, 7.0 Hz, 1 H), 1.19 (t, J=7.1 Hz, 3 H); LCMS RT = 5.56 min, m/z 439.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{23}H_{20}ClN_2O_3S$ [M+H$^+$] 439.0878, found 439.0884.

EXAMPLE 76. 10-ETHYL-11-OXO-N-(2-(TRIFLUOROMETHYL)BENZYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

[0254]

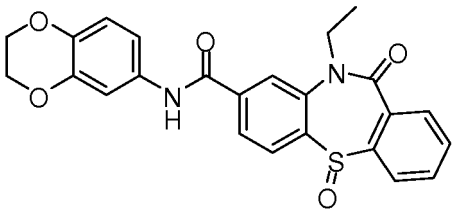


[0255] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.23 (t, J=5.8 Hz, 1 H), 8.05 (d, J=1.6 Hz, 1 H), 7.96 (dd, J=8.2, 1.6 Hz, 1 H), 7.67 - 7.74 (m, 3 H), 7.41 - 7.67 (m, 6 H), 4.50 - 4.72 (m, 3 H), 3.76 (dq, J=13.8, 7.1 Hz, 1 H), 1.19 (t, J=7.1 Hz, 3 H); ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -58.98 (s, 3 F); LCMS RT = 5.77 min, m/z 473.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{24}H_{20}F_3N_2O_3S$ [M+H$^+$] 473.1141, found

473.1149.

EXAMPLE 77. N-(2,3-DIHYDROBENZO[B][1,4]DIOXIN-6-YL)-10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

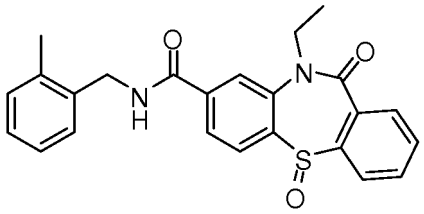
[0256]



[0257] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.15 (s, 1 H), 8.05 (d, J=1.6 Hz, 1 H), 7.94 (dd, J=8.2, 1.6 Hz, 1 H), 7.67 - 7.75 (m, 3 H), 7.62 - 7.67 (m, 1 H), 7.56 (td, J=7.4, 1.4 Hz, 1 H), 7.29 (d, J=2.5 Hz, 1 H), 7.10 (dd, J=8.8, 2.3 Hz, 1 H), 6.80 (d, J=8.8 Hz, 1 H), 4.59 (dq, J=14.0, 7.1 Hz, 1 H), 4.14 - 4.27 (m, 4 H), 3.78 (dq, J=13.8, 7.1 Hz, 1 H), 1.19 (t, J=7.1 Hz, 3 H); LCMS RT = 5.25 min, m/z 449.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{24}H_{21}N_2O_5S$ [M+H$^+$] 449.1166, found 449.1173.

EXAMPLE 78. 10-ETHYL-N-(2-METHYLBENZYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

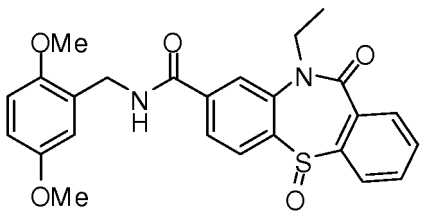
[0258]



[0259] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.00 (t, J=5.9 Hz, 1 H), 8.01 (d, J=1.2 Hz, 1 H), 7.93 (dd, J=7.8, 1.2 Hz, 1 H), 7.65 - 7.73 (m, 3 H), 7.60 - 7.65 (m, 1 H), 7.54 (td, J=7.6, 1.1 Hz, 1 H), 7.16 - 7.22 (m, 1 H), 7.06 - 7.16 (m, 3 H), 4.55 (dq, J=14.0, 7.1 Hz, 1 H), 4.33 - 4.48 (m, 2 H), 3.74 (dq, J=14.0, 7.0 Hz, 1 H), 2.27 (s, 3 H), 1.17 (t, J=7.1 Hz, 3 H); LCMS RT = 5.49 min, m/z 419.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{24}H_{23}N_2O_3S$ [M+H$^+$] 419.1424, found 419.1422.

EXAMPLE 79. N-(2,5-DIMETHOXYBENZYL)-10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

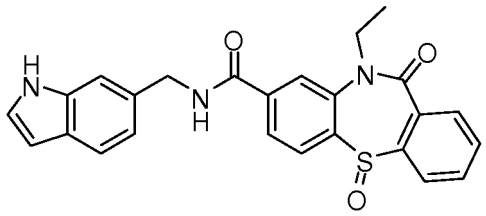
[0260]



[0261] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.95 (t, J=5.8 Hz, 1 H), 8.01 (d, J=1.4 Hz, 1 H), 7.93 (dd, J=8.1, 1.1 Hz, 1 H), 7.65 - 7.73 (m, 3 H), 7.59 - 7.65 (m, 1 H), 7.54 (td, J=7.5, 0.9 Hz, 1 H), 6.88 (d, J=8.8 Hz, 1 H), 6.69 - 6.79 (m, 2 H), 4.55 (dq, J=13.8, 7.0 Hz, 1 H), 4.27 - 4.44 (m, 2 H), 3.72 (s, 3 H), 3.68 - 3.84 (m, 1 H), 3.62 (s, 3 H), 1.18 (t, J=7.0 Hz, 3 H); LCMS RT = 5.32 min, m/z 465.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{25}H_{25}N_2O_5S$ [M+H$^+$] 465.1479, found 465.1472.

EXAMPLE 80. N-((1H-INDOL-6-YL)METHYL)-10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

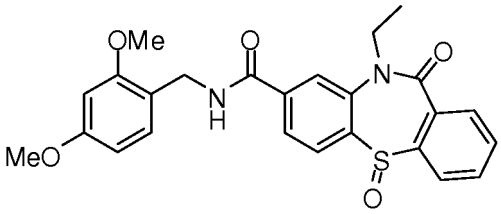
[0262]



[0263] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.98 (br. s., 1 H), 9.08 (t, J=6.0 Hz, 1 H), 8.01 (d, J=1.4 Hz, 1 H), 7.93 (dd, J=8.2, 1.2 Hz, 1 H), 7.64 - 7.73 (m, 3 H), 7.59 - 7.64 (m, 1 H), 7.53 (td, J=7.4, 1.1 Hz, 1 H), 7.43 (s, 1 H), 7.23 - 7.31 (m, 2 H), 7.01 (dd, J=8.3, 1.5 Hz, 1 H), 6.33 (t, J=2.5 Hz, 1 H), 4.40 - 4.63 (m, 3 H), 3.73 (dq, J=13.8, 7.0 Hz, 1 H), 1.16 (t, J=7.0 Hz, 3 H); LCMS RT = 5.07 min, m/z 444.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{25}H_{22}N_3O_3S$ [M+H$^+$] 444.1376, found 444.1368.

EXAMPLE 81. N-(2,4-DIMETHOXYBENZYL)-10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

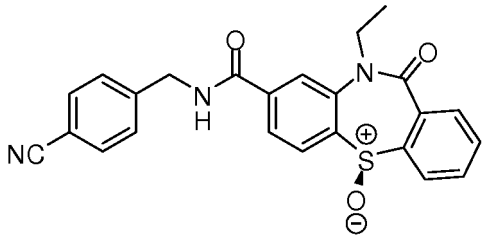
[0264]



[0265] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.87 (t, J=5.6 Hz, 1 H), 8.00 (d, J=1.4 Hz, 1 H), 7.91 (dd, J=8.2, 1.0 Hz, 1 H), 7.59 - 7.72 (m, 4 H), 7.54 (td, J=7.3, 1.1 Hz, 1 H), 7.06 (d, J=8.4 Hz, 1 H), 6.52 (d, J=2.3 Hz, 1 H), 6.42 (dd, J=8.3, 2.4 Hz, 1 H), 4.48 - 4.63 (m, 1 H), 4.24 - 4.38 (m, 2 H), 3.75 (s, 3 H), 3.70 (s, 3 H), 3.68 - 3.81 (m, 1 H), 1.17 (t, J=7.1 Hz, 3 H); LCMS RT = 5.35 min, m/z 465.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{25}H_{25}N_2O_5S$ [M+H$^+$] 465.1479, found 465.1456.

EXAMPLE 82. N-(4-CYANOBENZYL)-10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-(R)-OXIDE

[0266]

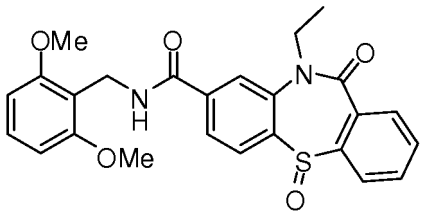


[0267] Separation of enantiomers via chiral HPLC: Analytical analysis was performed on a CHIRALAPK®AS® column (4.6 × 250 mm, 5 micron). The mobile phase was 100% of methanol at a flow rate of 1.0 mL/min with a run time of 15 minutes. The sample was detected with a diode array detector (DAD) at 220 nm and 254 nm. Optical rotation was determined with an in-line polarimeter (PDR-Chiral). The first eluting peak: RT = 5.95 minutes; positive optical rotation. The second eluting peak: RT = 9.08 minutes; negative optical rotation. Preparative separation was performed on a CHIRALAPK®AS® column (5× 50 cm, 20 micron). The mobile phase was 100% of methanol at a flow rate of 35 mL/min.

Fraction collection was triggered by UV absorbance (254 nm). LCMS RT = 5.13 min, m/z 430.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{24}H_{20}N_3O_3S$ [M+H$^+$] 430.1220, found 430.1223.

EXAMPLE 83. N-(2,6-DIMETHOXYBENZYL)-10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

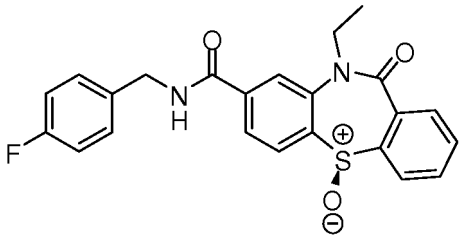
[0268]



[0269] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.32 (t, J=4.2 Hz, 1 H), 7.92 (d, J=1.4 Hz, 1 H), 7.87 (dd, J=8.0, 1.2 Hz, 1 H), 7.64 - 7.73 (m, 2 H), 7.58 - 7.64 (m, 2 H), 7.53 (td, J=7.4, 1.3 Hz, 1 H), 7.23 (t, J=8.4 Hz, 1 H), 6.63 (d, J=8.4 Hz, 2 H), 4.52 (td, J=13.8, 6.7 Hz, 1 H), 4.39 (dd, J=4.3, 2.2 Hz, 2 H), 3.72 (s, 6 H), 3.63 - 3.80 (m, 1 H), 1.15 (t, J=7.1 Hz, 3 H); LCMS RT = 5.42 min, m/z 465.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{25}H_{25}N_2O_5S$ [M+H$^+$] 465.1479, found 465.1480.

EXAMPLE 84. 10-ETHYL-N-(4-FLUOROBENZYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-(R)-OXIDE

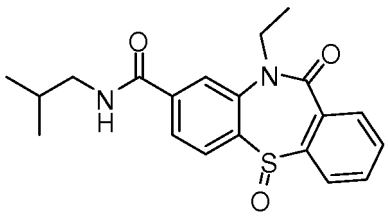
[0270]



[0271] Separation of enantiomers via chiral HPLC: Analytical analysis was performed on a CHIRALCEL®OJ® column (4.6 × 250 mm, 5 micron). The mobile phase was 100% of methanol at a flow rate of 1.0 mL/min with a run time of 15 minutes. The sample was detected with a diode array detector (DAD) at 220 nm and 254 nm. Optical rotation was determined with an in-line polarimeter (PDR-Chiral). The first eluting peak: RT = 6.26 minutes; negative optical rotation. The second eluting peak: RT = 6.86 minutes; positive optical rotation. Preparative separation was performed on a CHIRALCEL®OJ® column (5× 50 cm, 20 micron). The mobile phase was 100% of methanol at a flow rate of 35 mL/min. Fraction collection was triggered by UV absorbance (254 nm). LCMS RT = 5.43 min, m/z 423.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{23}H_{20}FN_2O_3S$ [M+H$^+$] 423.1173, found 423.1179.

EXAMPLE 85. 10-ETHYL-N-ISOBUTYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

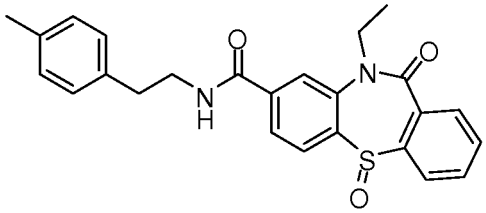
[0272]



[0273] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.56 (t, J=5.9 Hz, 1 H), 7.95 (d, J=1.4 Hz, 1 H), 7.87 (dd, J=8.1, 1.3 Hz, 1 H), 7.59 - 7.72 (m, 4 H), 7.54 (td, J=7.5, 1.3 Hz, 1 H), 4.55 (dq, J=14.1, 7.1 Hz, 1 H), 3.74 (dq, J=13.8, 7.1 Hz, 1 H), 2.92 - 3.13 (m, 2 H), 1.77 (tt, J=13.5, 6.8 Hz, 1 H), 1.17 (t, J=7.1 Hz, 3 H), 0.84 (d, J=6.7 Hz, 6 H); LCMS RT = 5.06 min, m/z 371.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{20}H_{23}N_2O_3S$ [M+H$^+$] 371.1424, found 371.1429.

EXAMPLE 86. 10-ETHYL-N-(4-METHYLPHENETHYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

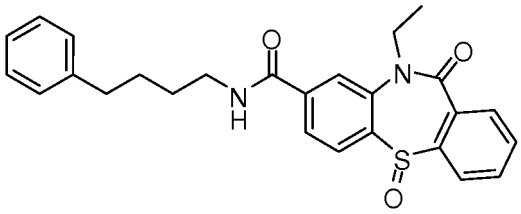
[0274]



[0275] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.66 (t, J=5.5 Hz, 1 H), 7.90 (d, J=1.4 Hz, 1 H), 7.84 (dd, J=8.1, 1.1 Hz, 1 H), 7.60 - 7.72 (m, 4 H), 7.54 (td, J=7.4, 1.4 Hz, 1 H), 7.03 - 7.10 (m, 4 H), 4.54 (dq, J=14.0, 7.1 Hz, 1 H), 3.72 (dddd, J=13.7, 7.2, 7.1, 6.9 Hz, 1 H), 3.35 - 3.48 (m, 2 H), 2.73 (t, J=7.3 Hz, 2 H), 2.23 (s, 3 H), 1.18 (t, J=7.0 Hz, 3 H); LCMS RT = 5.67 min, m/z 433.2 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{25}H_{25}N_2O_3S$ [M+H$^+$] 433.1580, found 433.1581.

EXAMPLE 87. 10-ETHYL-11-OXO-N-(4-PHENYLBUTYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

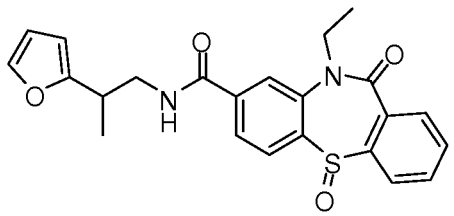
[0276]



[0277] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.56 (t, J=5.7 Hz, 1 H), 7.93 (d, J=1.6 Hz, 1 H), 7.85 (dd, J=8.2, 1.4 Hz, 1 H), 7.59 - 7.75 (m, 4 H), 7.54 (td, J=7.4, 1.3 Hz, 1 H), 7.19 - 7.26 (m, 2 H), 7.08 - 7.18 (m, 3 H), 4.55 (dq, J=14.0, 7.1 Hz, 1 H), 3.72 (dq, J=13.9, 7.0 Hz, 1 H), 3.15 - 3.27 (m, 2 H), 2.55 (t, J=7.3 Hz, 2 H), 1.51 - 1.62 (m, 2 H), 1.42 - 1.51 (m, 2 H), 1.17 (t, J=7.0 Hz, 3 H); LCMS RT = 5.91 min, m/z 447.2 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{26}H_{27}N_2O_3S$ [M+H$^+$] 447.1737, found 447.1737.

EXAMPLE 88. 10-ETHYL-N-(2-(FURAN-2-YL)PROPYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

[0278]

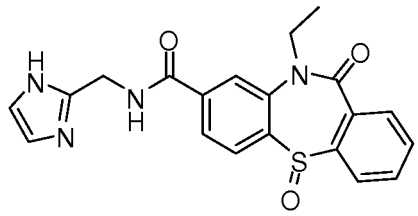


[0279] The title compound was prepared according to the general protocol A. LCMS RT = 5.21 min, m/z 423.1 [M+H$^+$];

HRMS (ESI) m/z calcd for $C_{23}H_{23}N_2O_4S$ [M+H$^+$] 423.1373, found 423.1381.

EXAMPLE 89. N-((1H-IMIDAZOL-2-YL)METHYL)-10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

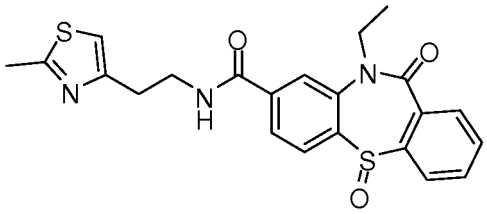
[0280]



[0281] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.75 (br. s., 1 H), 9.11 (t, J=5.7 Hz, 1 H), 8.02 (d, J=1.4 Hz, 1 H), 7.93 (dd, J=8.3, 1.3 Hz, 1 H), 7.69 (t, J=7.7 Hz, 3 H), 7.59 - 7.65 (m, 1 H), 7.54 (td, J=7.5, 1.3 Hz, 1 H), 6.97 (s, 1 H), 6.77 (s, 1 H), 4.56 (td, J=13.9, 7.0 Hz, 1 H), 4.36 - 4.51 (m, 2 H), 3.74 (td, J=13.9, 6.7 Hz, 1 H), 1.18 (t, J=7.1 Hz, 3 H); LCMS RT = 3.43 min, m/z 395.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{20}H_{19}N_4O_3S$ [M+H$^+$] 395.1172, found 395.1180.

EXAMPLE 90. 10-ETHYL-N-(2-(2-METHYLTHIAZOL-4-YL)ETHYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

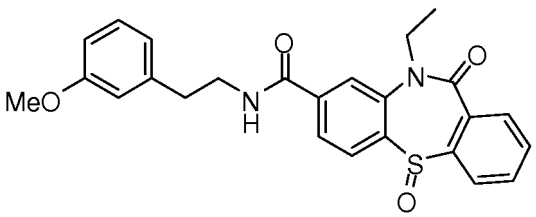
[0282]



[0283] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.69 (t, J=5.6 Hz, 1 H), 7.92 (d, J=1.6 Hz, 1 H), 7.85 (dd, J=8.2, 1.4 Hz, 1 H), 7.59 - 7.75 (m, 4 H), 7.49 - 7.58 (m, 1 H), 7.12 (s, 1 H), 4.55 (dq, J=13.9, 7.0 Hz, 1 H), 3.73 (dq, J=13.8, 6.9 Hz, 1 H), 3.40 - 3.58 (m, 2 H), 2.85 (t, J=7.3 Hz, 2 H), 2.58 (s, 3 H), 1.17 (t, J=7.0 Hz, 3 H); LCMS RT = 4.15 min, m/z 440.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{22}H_{22}N_3O_3S_2$ [M+H$^+$] 440.1097, found 440.1105.

EXAMPLE 91. 10-ETHYL-N-(3-METHOXYPHENETHYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

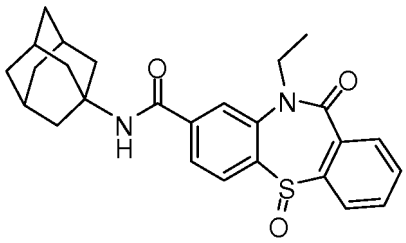
[0284]



[0285] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.67 (t, J=5.6 Hz, 1 H), 7.90 (d, J=1.4 Hz, 1 H), 7.84 (dd, J=8.3, 1.3 Hz, 1 H), 7.59 - 7.74 (m, 4 H), 7.50 - 7.58 (m, 1 H), 7.16 (t, J=7.9 Hz, 1 H), 6.65 - 6.82 (m, 3 H), 4.46 - 4.62 (m, 1 H), 3.69 - 3.78 (m, 1 H), 3.66 (s, 3 H), 3.37 - 3.49 (m, 2 H), 2.76 (t, J=7.2 Hz, 2 H), 1.17 (t, J=7.0 Hz, 3 H); LCMS RT = 5.36 min, m/z 449.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{25}H_{25}N_2O_4S$ [M+H$^+$] 449.1530, found 449.1528.

EXAMPLE 92. N-(1-ADAMANTYL)-10-ETHYL-11-oxo-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

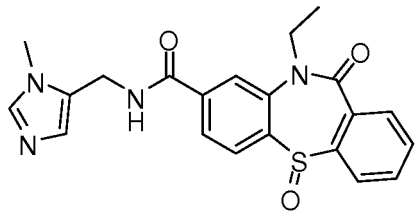
[0286]



[0287] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.07 (d, J=6.8 Hz, 1 H), 7.92 (d, J=1.4 Hz, 1 H), 7.83 (dd, J=8.1, 1.1 Hz, 1 H), 7.58 - 7.73 (m, 4 H), 7.48 - 7.57 (m, 1 H), 4.57 (dq, J=13.9, 7.0 Hz, 1 H), 3.91 - 4.02 (m, 1 H), 3.75 (dq, J=14.0, 7.0 Hz, 1 H), 2.04 (t, J=14.2 Hz, 2 H), 1.92 (br. s., 2 H), 1.70 - 1.85 (m, 6 H), 1.67 (br. s., 2 H), 1.40 - 1.53 (m, 2 H), 1.17 (t, J=7.1 Hz, 3 H); LCMS RT = 6.23 min, m/z 449.2 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{26}H_{29}N_2O_3S$ [M+H$^+$] 449.1893, found 449.1892.

EXAMPLE 93. 10-ETHYL-N-((1-METHYL-1H-IMIDAZOL-5-YL)METHYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

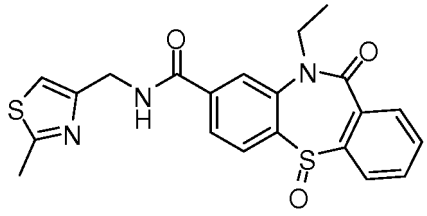
[0288]



[0289] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.12 (t, J=5.7 Hz, 1 H), 8.89 (s, 1 H), 7.98 (d, J=1.4 Hz, 1 H), 7.89 (dd, J=8.2, 1.0 Hz, 1 H), 7.65 - 7.75 (m, 3 H), 7.59 - 7.65 (m, 1 H), 7.48 - 7.58 (m, 2 H), 4.40 - 4.66 (m, 3 H), 3.79 (s, 3 H), 3.65 - 3.77 (m, 1 H), 1.17 (t, J=7.1 Hz, 3 H); LCMS RT = 3.49 min, m/z 409.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{21}H_{21}N_4O_3S$ [M+H$^+$] 409.1329, found 409.1331.

EXAMPLE 94. 10-ETHYL-N-((2-METHYLTHIAZOL-4-YL)METHYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

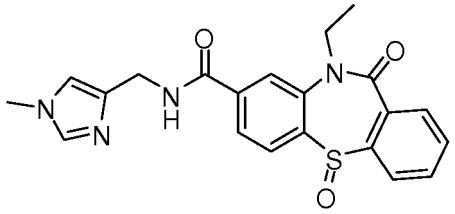
[0290]



[0291] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.15 (t, J=5.8 Hz, 1 H), 8.02 (d, J=1.6 Hz, 1 H), 7.86 - 7.96 (m, 1 H), 7.60 - 7.73 (m, 4 H), 7.51 - 7.57 (m, 1 H), 7.21 (s, 1 H), 4.52 - 4.62 (m, 1 H), 4.38 - 4.52 (m, 2 H), 3.68 - 3.83 (m, 1 H), 2.58 (s, 3 H), 1.18 (t, J=7.0 Hz, 3 H); LCMS RT = 4.42 min, m/z 426.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{21}H_{20}N_3O_3S_2$ [M+H$^+$] 426.0941, found 426.0945.

EXAMPLE 95. 10-ETHYL-N-((1-METHYL-1H-IMIDAZOL-4-YL)METHYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

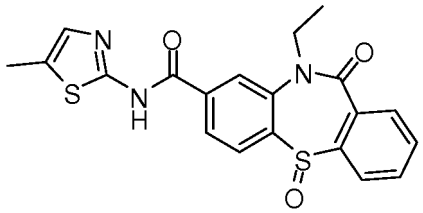
[0292]



[0293] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.18 (t, J=5.6 Hz, 1 H), 8.72 (br. s., 1 H), 7.99 (d, J=1.6 Hz, 1 H), 7.90 (dd, J=8.2, 1.2 Hz, 1 H), 7.66 - 7.77 (m, 3 H), 7.59 - 7.65 (m, 1 H), 7.50 - 7.59 (m, 1 H), 7.45 (s, 1 H), 4.51 - 4.64 (m, 1 H), 4.33 - 4.50 (m, 2 H), 3.74 (s, 3 H), 3.61 - 3.82 (m, 1 H), 1.18 (t, J=7.1 Hz, 3 H); LCMS RT = 3.48 min, m/z 409.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{21}H_{21}N_4O_3S$ [M+H$^+$] 409.1329, found 409.1339.

EXAMPLE 96. 10-ETHYL-N-(5-METHYLTHIAZOL-2-YL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

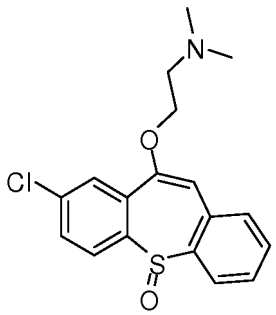
[0294]



[0295] The title compound was prepared according to the general protocol B. LCMS RT = 5.17 min, m/z 412.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{20}H_{18}N_3O_3S_2$ [M+H$^+$] 412.0784, found 412.0793.

EXAMPLE 97. (E)-2-(8-CHLORODIBENZO[B,F]THIEPIN-10-YLOXY)-N,N-DIMETHYLETHANAMINE 5-OXIDE

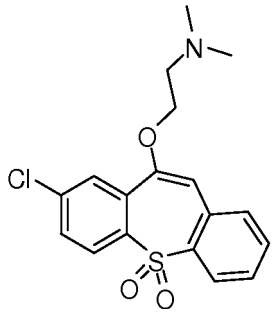
[0296]



[0297] A suspension of 2-(8-chlorodibenzo[b,f]thiepin-10-yloxy)-N,N-dimethylethanamine (5.00 mg, 0.015 mmol) in acetic acid (1.00 mL) was treated at room temperature with H_2O_2 (69.0 μL, 0.68 mmol). The reaction mixture was stirred at room temperature for overnight. The crude mixture was concentrated and purified by preparative HPLC to give 1.7 mg (32%) of the title compound and 1.7 mg (31%) of (E)-2-(8-chlorodibenzo[b,f]thiepin-10-yloxy)-N,N-dimethylethanamine 5,5-dioxide (XJB08-083_pk2, NCGC00241701-01). LCMS RT = 4.04 min, m/z 348.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{18}H_{19}ClNO_2S$ [M+H$^+$] 348.0820, found 348.0820.

EXAMPLE 98. (E)-2-(8-CHLORODIBENZO[B,F]THIEPIN-10-YLOXY)-N,N-DIMETHYLETHANAMINE 5,5-DIOXIDE

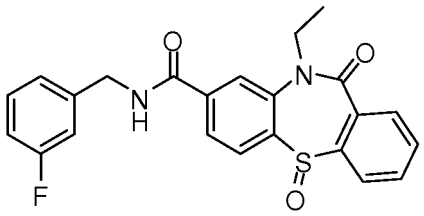
[0298]



[0299] LCMS RT = 4.23 min, m/z 364.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{18}H_{19}ClNO_3S$ [M+H$^+$] 364.0769, found 364.0770.

EXAMPLE 99. 10-ETHYL-N-(3-FLUOROBENZYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

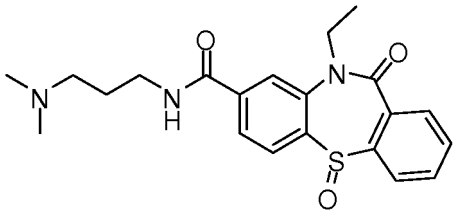
[0300]



[0301] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.18 (t, J=6.3 Hz, 1 H), 8.02 (d, J=1.6 Hz, 1 H), 7.93 (dd, J=8.2, 1.6 Hz, 1 H), 7.66 - 7.75 (m, 3 H), 7.61 - 7.67 (m, 1 H), 7.55 (ddd, J=7.9, 7.0, 1.4 Hz, 1 H), 7.27 - 7.38 (m, 1 H), 6.98 - 7.16 (m, 3 H), 4.51 - 4.65 (m, 1 H), 4.36 - 4.51 (m, 2 H), 3.66 - 3.83 (m, 1 H), 1.18 (t, J=7.1 Hz, 3 H); LCMS RT = 5.33 min, m/z 423.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{23}H_{20}FN_2O_3S$ [M+H$^+$] 423.1173, found 423.1177.

EXAMPLE 100. N-(3-(DIMETHYLAMINO)PROPYL)-10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

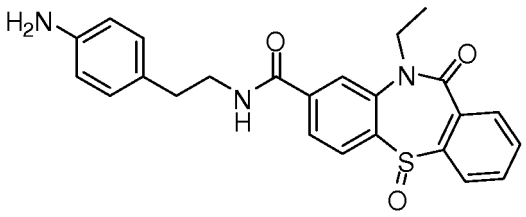
[0302]



[0303] The title compound was prepared according to the general protocol B. LCMS RT = 3.48 min, m/z 400.2 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{21}H_{26}N_3O_3S$ [M+H$^+$] 400.1689, found 400.1692.

EXAMPLE 101. N-(4-AMINOPEENETHYL)-10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4] THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

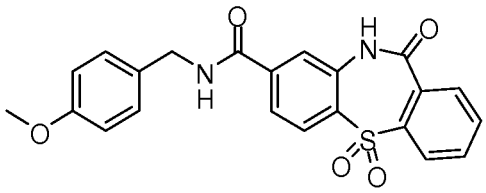
[0304]



[0305] The title compound was prepared according to the general protocol B. LCMS RT = 3.69 min, m/z 434.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{24}H_{24}N_3O_3S$ [M+H$^+$] 434.1533, found 434.1533.

EXAMPLE 102. N-(4-METHOXYBENZYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5,5-DIOXIDE

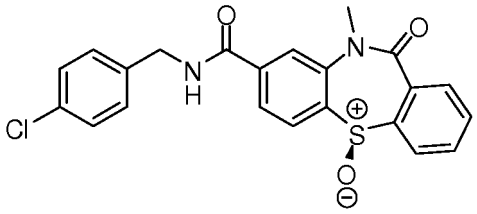
[0306]



[0307] A suspension of N-(4-methoxybenzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide (25.0 mg, 0.064 mmol) in acetic acid (2.00 mL) was treated at room temperature with H_2O_2 (0.60 mL, 5.87 mmol). The reaction mixture was stirred at room temperature for 5 days. $Na_2S_2O_3$ was added to the solution to quench the excess H_2O_2. Acetic acid was removed and the crude mixture was purified by preparative HPLC to give 6.7 mg (24%) the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.48 (s, 1 H), 9.17 (t, J=6.0 Hz, 1 H), 8.02 (d, J=8.2 Hz, 1 H), 7.91 - 7.99 (m, 2 H), 7.75 - 7.92 (m, 4 H), 7.15 - 7.26 (m, 2 H), 6.79 - 6.92 (m, 2 H), 4.36 (d, J=5.9 Hz, 2 H), 3.69 (s, 3 H); LCMS RT = 4.98 min, m/z 423.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{22}H_{19}N_2O_5S$ [M+H$^+$] 423.1009, found 423.1005.

EXAMPLE 103. N-(4-CHLOROBENZYL)-10-METHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-(R)-OXIDE

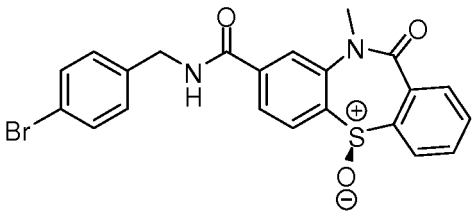
[0308]



[0309] Separation of enantiomers via chiral HPLC: Analytical analysis was performed on a CHIRALPAK®IA® column (4.6 $\times$ 150 mm, 5 micron). The mobile phase was 60% of isopropanol in hexanes at a flow rate of 1.0 mL/min with a run time of 15 minutes. The sample was detected with a diode array detector (DAD) at 220 nm and 254 nm. Optical rotation was determined with an in-line polarimeter (PDR-Chiral). The first eluting peak: RT = 5.96 minutes; positive optical rotation. The second eluting peak: RT = 6.72 minutes; negative optical rotation. Preparative separation was performed on a CHIRALPAK®IA® column (5$\times$ 50 cm, 20 micron). The mobile phase was 60% of isopropanol in hexanes at a flow rate of 30 mL/min. Fraction collection was triggered by UV absorbance (254 nm). LCMS RT = 5.47 min, m/z 425.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{22}H_{18}ClN_2O_3S$ [M+H$^+$] 425.0721, found 425.0714.

EXAMPLE 104. N-(4-BROMOBENZYL)-10-METHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-(R)-OXIDE

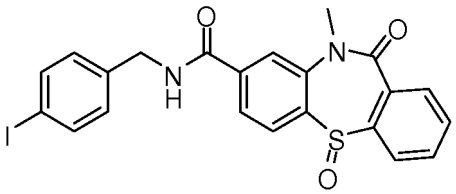
[0310]



[0311] Separation of enantiomers via chiral HPLC: Analytical analysis was performed on a CHIRALPAK®IA® column (4.6 × 250 mm, 5 micron). The mobile phase was 60% of ethanol in hexanes at a flow rate of 1.0 mL/min with a run time of 15 minutes. The sample was detected with a diode array detector (DAD) at 220 nm and 254 nm. Optical rotation was determined with an in-line polarimeter (PDR-Chiral). The first eluting peak: RT = 7.49 minutes; positive optical rotation. The second eluting peak: RT = 8.68 minutes; negative optical rotation. Preparative separation was performed on a CHIRALPAK®IA® column (5× 50 cm, 20 micron). The mobile phase was 60% of ethanol in hexanes at a flow rate of 35 mL/min. Fraction collection was triggered by UV absorbance (254 nm). LCMS RT = 5.57 min, m/z 469.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{22}H_{18}BrN_2O_3S$ [M+H$^+$] 469.0216, found 469.0220.

EXAMPLE 105. N-(4-IODOBENZYL)-10-METHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

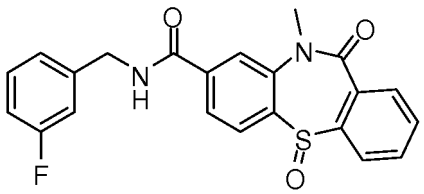
[0312]



[0313] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.16 (t, J=6.1 Hz, 1 H), 8.00 (d, J=1.6 Hz, 1 H), 7.86 - 7.95 (m, 1 H), 7.70 - 7.77 (m, 2 H), 7.61 - 7.69 (m, 4 H), 7.57 (ddd, J=7.9, 7.0, 1.4 Hz, 1 H), 7.05 - 7.14 (m, 2 H), 4.29 - 4.50 (m, 2 H), 3.55 (s, 3 H); LCMS RT = 5.71 min, m/z 517.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{22}H_{18}IN_2O_3S$ [M+H$^+$] 517.0077, found 517.0078.

EXAMPLE 106. N-(3-FLUOROBENZYL)-10-METHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

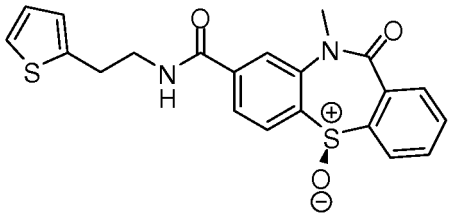
[0314]



[0315] The title compound was prepared according to the general protocol A. LCMS RT = 5.18 min, m/z 431.0 [M+Na$^+$]; HRMS (ESI) m/z calcd for $C_{22}H_{18}FN_2O_3S$ [M+H$^+$] 409.1017, found 409.1019.

EXAMPLE 107. 10-METHYL-11-OXO-N-(2-(THIOPHEN-2-YL)ETHYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-(R)-OXIDE

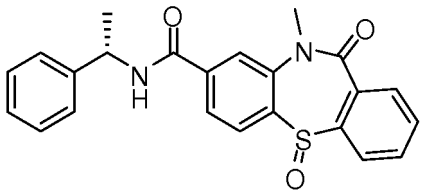
[0316]



[0317] Separation of enantiomers via chiral HPLC: Analytical analysis was performed on a CHIRALPAK®IA® column (4.6 × 250 mm, 5 micron). The mobile phase was 60% of ethanol in hexanes at a flow rate of 1.0 mL/min with a run time of 15 minutes. The sample was detected with a diode array detector (DAD) at 220 nm and 254 nm. Optical rotation was determined with an in-line polarimeter (PDR-Chiral). The first eluting peak: RT = 6.51 minutes; negative optical rotation. The second eluting peak: RT = 6.76 minutes; positive optical rotation. Preparative separation was performed on a CHIRALPAK®IA® column (5× 50 cm, 20 micron). The mobile phase was 60% of ethanol in hexanes at a flow rate of 35 mL/min. Fraction collection was triggered by UV absorbance (254 nm). LCMS RT = 5.10 min, m/z 411.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_3S_2$ [M+H$^+$] 411.0832, found 411.0833.

EXAMPLE 108. (S)-10-METHYL-11-OXO-N-(1-PHENYLETHYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

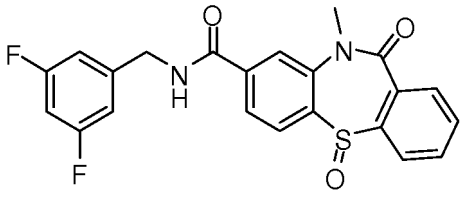
[0318]



[0319] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.90 (d, J=8.0 Hz, 0.5 H), 8.89 (d, J=8.0 Hz, 0.5 H), 7.99 (dd, J=6.8, 1.6 Hz, 1 H), 7.91 (td, J=8.1, 1.6 Hz, 1 H), 7.70 - 7.77 (m, 2 H), 7.63 - 7.68 (m, 2 H), 7.56 (tt, J=7.4, 1.3 Hz, 1 H), 7.31 - 7.37 (m, 2 H), 7.25 - 7.31 (m, 2 H), 7.16 - 7.22 (m, 1 H), 5.11 (quin, J=7.1 Hz, 1 H), 3.56 (s, 1.5 H), 3.55 (s, 1.5 H), 1.44 (d, J=7.0 Hz, 1.5 H), 1.43 (d, J=7.0 Hz, 1.5 H); LCMS RT = 5.29 min, m/z 405.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{23}H_{21}N_2O_3S$ [M+H$^+$] 405.1267, found 405.1265.

EXAMPLE 109. N-(3,5-DIFLUOROBENZYL)-10-METHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

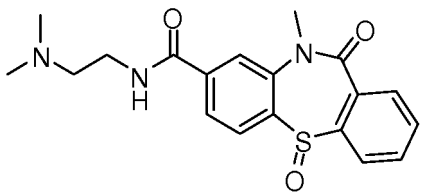
[0320]



[0321] The title compound was prepared according to the general protocol A. LCMS RT = 5.34 min, m/z 449.0 [M+Na$^+$]; HRMS (ESI) m/z calcd for $C_{22}H_{17}F_2N_2O_3S$ [M+H$^+$] 427.0922, found 427.0919.

EXAMPLE 110. N-(2-(DIMETHYLAMINO)ETHYL)-10-METHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

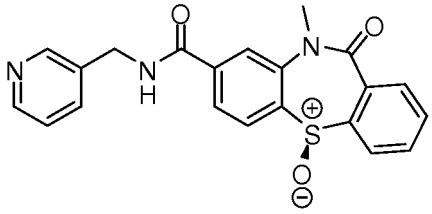
[0322]



[0323] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.78 (t, J=5.7 Hz, 1 H), 7.96 (d, J=1.6 Hz, 1 H), 7.89 (dd, J=8.1, 1.5 Hz, 1 H), 7.69 - 7.79 (m, 3 H), 7.62 - 7.69 (m, 1 H), 7.51 - 7.61 (m, 1 H), 3.56 (s, 3 H), 3.44 - 3.69 (m, 2 H), 3.20 (br. s., 2 H), 2.79 (s, 6 H); LCMS RT = 3.18 min, m/z 372.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{19}H_{22}N_3O_3S$ [M+H$^+$] 372.1376, found 372.1382.

EXAMPLE 111. 10-METHYL-11-OXO-N-(PYRIDIN-3-YLMETHYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-(R)-OXIDE

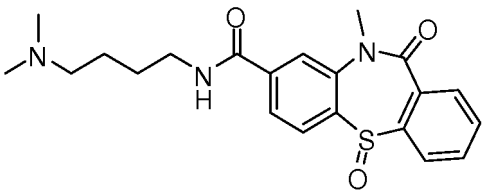
[0324]



[0325] Separation of enantiomers via chiral HPLC: Analytical analysis was performed on a CHIRALPAK®IA® column (4.6 $\times$ 250 mm, 5 micron). The mobile phase was 60% of ethanol in hexanes at a flow rate of 1.0 mL/min with a run time of 15 minutes. The sample was detected with a diode array detector (DAD) at 220 nm and 254 nm. Optical rotation was determined with an in-line polarimeter (PDR-Chiral). The first eluting peak: RT = 9.00 minutes; positive optical rotation. The second eluting peak: RT = 13.28 minutes; negative optical rotation. Preparative separation was performed on a CHIRALPAK®IA® IA column (5$\times$ 50 cm, 20 micron). The mobile phase was 60% of ethanol in hexanes at a flow rate of 35 mL/min. Fraction collection was triggered by UV absorbance (254 nm). LCMS RT = 3.37 min, m/z 392.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{21}H_{18}N_3O_3S$ [M+H$^+$] 392.1063, found 392.1068.

EXAMPLE 112. N-(4-(DIMETHYLAMINO)BUTYL)-10-METHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

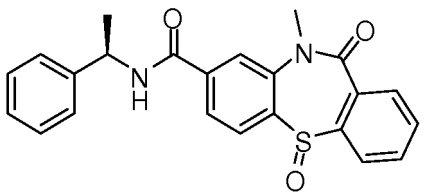
[0326]



[0327] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.63 (t, J=5.8 Hz, 1 H), 7.94 (d, J=1.6 Hz, 1 H), 7.86 (dd, J=8.2, 1.6 Hz, 1 H), 7.70 - 7.78 (m, 2 H), 7.63 - 7.70 (m, 2 H), 7.57 (ddd, J=7.9, 7.0, 1.4 Hz, 1 H), 3.56 (s, 3 H), 3.18 - 3.36 (m, 2 H), 2.93 - 3.10 (m, 2 H), 2.72 (s, 6 H), 1.55 - 1.68 (m, 2 H), 1.41 - 1.54 (m, 2 H); LCMS RT = 3.27 min, m/z 400.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{21}H_{26}N_3O_3S$ [M+H$^+$] 400.1689, found 400.1694.

EXAMPLE 113. (R)-10-METHYL-11-OXO-N-(1-PHENYLETHYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

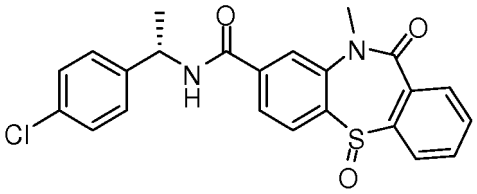
[0328]



[0329] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.90 (d, J=8.1 Hz, 0.5 H), 8.89 (d, J=8.1 Hz, 0.5 H), 7.99 (dd, J=6.9, 1.3 Hz, 1 H), 7.91 (td, J=8.1, 1.6 Hz, 1 H), 7.69 - 7.77 (m, 2 H), 7.63 - 7.69 (m, 2 H), 7.56 (tt, J=7.5, 1.3 Hz, 1 H), 7.24 - 7.38 (m, 4 H), 7.16 - 7.23 (m, 1 H), 5.11 (qd, J=7.4, 7.1 Hz, 1 H), 3.56 (s, 1.5 H), 3.55 (s, 1.5 H), 1.45 (d, J=7.0 Hz, 1.5 H), 1.44 (d, J=7.0 Hz, 1.5 H); LCMS RT = 5.28 min, m/z 405.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{23}H_{21}N_2O_3S$ [M+H$^+$] 405.1267, found 405.1270.

EXAMPLE 114. (S)-N-(1-(4-CHLOROPHENYL)ETHYL)-10-METHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

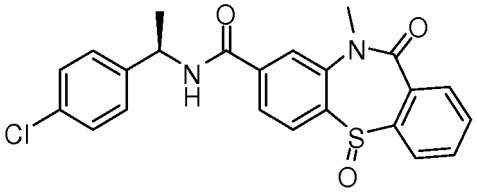
[0330]



[0331] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.92 (d, J=7.7 Hz, 0.5 H), 8.91 (d, J=7.7 Hz, 0.5 H), 7.98 (dd, J=7.8, 1.4 Hz, 1 H), 7.90 (td, J=8.1, 1.6 Hz, 1 H), 7.70 - 7.77 (m, 2 H), 7.62 - 7.69 (m, 2 H), 7.53 - 7.61 (m, 1 H), 7.30 - 7.41 (m, 4 H), 5.09 (quin, J=7.1 Hz, 1 H), 3.56 (s, 1.5 H), 3.55 (s, 1.5 H), 1.43 (d, J=7.1 Hz, 1.5 H), 1.42 (d, J=7.1 Hz, 1.5 H); LCMS RT = 5.69 min, m/z 439.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{23}H_{20}ClN_2O_3S$ [M+H$^+$] 439.0878, found 439.0885.

EXAMPLE 115. (R)-N-(1-(4-CHLOROPHENYL)ETHYL)-10-METHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

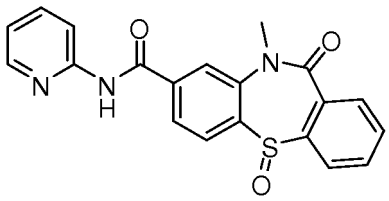
[0332]



[0333] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.92 (d, J=7.7 Hz, 0.5 H), 8.91 (d, J=7.7 Hz, 0.5 H), 7.98 (dd, J=7.9, 1.5 Hz, 1 H), 7.90 (td, J=8.1, 1.6 Hz, 1 H), 7.70 - 7.77 (m, 2 H), 7.63 - 7.69 (m, 2 H), 7.53 - 7.61 (m, 1 H), 7.29 - 7.39 (m, 4 H), 5.09 (quin, J=7.3 Hz, 1 H), 3.56 (s, 1.5 H), 3.55 (s, 1.5 H), 1.43 (d, J=7.0 Hz, 1.5 H), 1.42 (d, J=7.0 Hz, 1.5 H); LCMS RT = 5.69 min, m/z 439.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{23}H_{20}ClN_2O_3S$ [M+H$^+$] 439.0878, found 439.0878.

EXAMPLE 116. 10-METHYL-11-OXO-N-(PYRIDIN-2-YL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

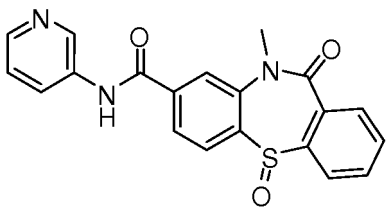
[0334]



[0335] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.01 (s, 1 H), 8.37 (ddd, J=4.9, 2.0, 1.0 Hz, 1 H), 8.17 (d, J=1.6 Hz, 1 H), 8.14 (d, J=8.4 Hz, 1 H), 8.01 (dd, J=8.1, 1.7 Hz, 1 H), 7.83 (ddd, J=8.3, 7.3, 2.0 Hz, 1 H), 7.66 - 7.78 (m, 4 H), 7.58 (td, J=7.4, 1.4 Hz, 1 H), 7.16 (ddd, J=7.4, 4.8, 1.1 Hz, 1 H), 3.60 (s, 3 H); LCMS RT = 3.99 min, m/z 378.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{20}H_{16}N_3O_3S$ [M+H$^+$] 378.0907, found 378.0908.

EXAMPLE 117. 10-METHYL-11-OXO-N-(PYRIDIN-3-YL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

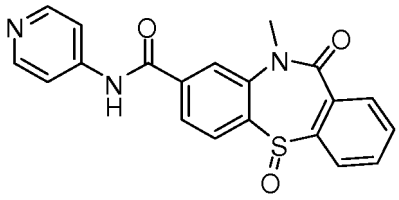
[0336]



[0337] The title compound was prepared according to the general protocol B. LCMS RT = 3.43 min, m/z 378.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{20}H_{16}N_3O_3S$ [M+H$^+$] 378.0907, found 378.0909.

EXAMPLE 118. 10-METHYL-11-OXO-N-(PYRIDIN-4-YL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

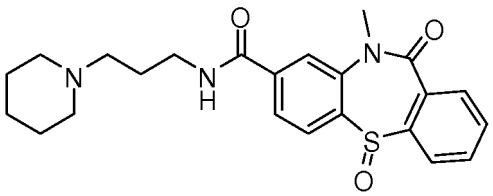
[0338]



[0339] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.21 (br. s., 1 H), 8.65 (d, J=6.7 Hz, 2 H), 8.11 (d, J=1.4 Hz, 1 H), 7.94 - 8.06 (m, 3 H), 7.65 - 7.82 (m, 4 H), 7.58 (td, J=7.5, 1.5 Hz, 1 H), 3.59 (s, 3 H); LCMS RT = 3.44 min, m/z 378.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{20}H_{16}N_3O_3S$ [M+H$^+$] 378.0907, found 378.0906.

EXAMPLE 119. 10-METHYL-11-OXO-N-(3-(PIPERIDIN-1-YL)PROPYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

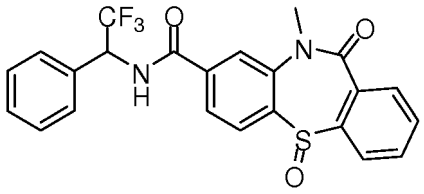
[0340]



[0341] The title compound was prepared according to the general protocol B. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.72 (t, J=5.6 Hz, 1 H), 7.95 (d, J=1.4 Hz, 1 H), 7.87 (dd, J=8.2, 1.6 Hz, 1 H), 7.63 - 7.79 (m, 4 H), 7.57 (td, J=7.4, 1.3 Hz, 1 H), 3.55 (s, 3 H), 3.21 - 3.45 (m, 4 H), 2.97 - 3.10 (m, 2 H), 2.71 - 2.91 (m, 2 H), 1.72 - 1.92 (m, 4 H), 1.45 - 1.72 (m, 3 H), 1.25 - 1.43 (m, 1 H); LCMS RT = 3.41 min, m/z 426.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{23}H_{28}N_3O_3S$ [M+H$^+$] 426.1846, found 426.1854.

EXAMPLE 120. 10-METHYL-11-OXO-N-(2,2,2-TRIFLUORO-1-PHENYLETHYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

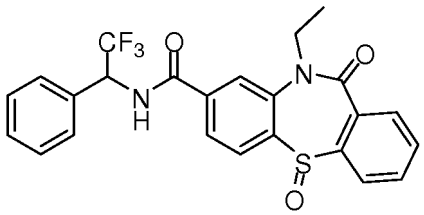
[0342]



[0343] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.61 (d, J=9.2 Hz, 0.5 H), 9.59 (d, J=9.2 Hz, 0.5 H), 7.99 (t, J=1.9 Hz, 1 H), 7.91 (ddd, J=8.1, 5.1, 1.7 Hz, 1 H), 7.65 - 7.78 (m, 4 H), 7.60 - 7.65 (m, 2 H), 7.53 - 7.60 (m, 1 H), 7.37 - 7.46 (m, 3 H), 5.94 - 6.08 (m, 1 H), 3.57 (s, 1.5 H), 3.56 (s, 1.5 H); ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -71.85 (d, J=8.9 Hz, 1.5 F), -71.91 (d, J=8.9 Hz, 1.5 F); LCMS RT = 5.76 min, m/z 459.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{23}H_{18}F_3N_2O_3S$ [M+H$^+$] 459.0985, found 459.0991.

EXAMPLE 121. 10-ETHYL-11-OXO-N-(2,2,2-TRIFLUORO-1-PHENYLETHYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

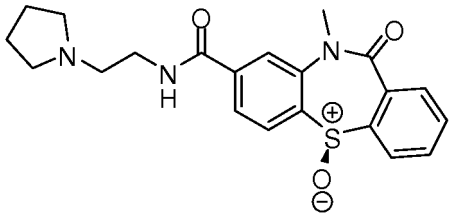
[0344]



[0345] The title compound was prepared according to the general protocol A. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.61 (d, J=6.9 Hz, 0.5 H), 9.59 (d, J=6.9 Hz, 0.5 H), 8.01 (dd, J=4.4, 1.5 Hz, 1 H), 7.92 (ddd, J=8.1, 4.1, 1.6 Hz, 1 H), 7.67 - 7.75 (m, 3 H), 7.59 - 7.67 (m, 3 H), 7.52 - 7.59 (m, 1 H), 7.37 - 7.46 (m, 3 H), 6.01 (quin, J=9.0 Hz, 1 H), 4.49 - 4.64 (m, J=13.9, 7.2, 7.2, 7.0, 3.4 Hz, 1 H), 3.57 - 3.99 (m, 1 H), 1.19 (t, J=7.1 Hz, 1.5 H), 1.18 (t, J=7.1 Hz, 1.5 H); ^{19}F NMR (376 MHz, DMSO-d_6) δ ppm -71.85 (d, J=8.9 Hz, 1.5 F), -71.90 (d, J=8.3 Hz, 1.5 F); LCMS RT = 6.00 min, m/z 473.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{24}H_{20}F_3N_2O_3S$ [M+H$^+$] 473.1141, found 473.1147.

EXAMPLE 122. 10-METHYL-11-OXO-N-(2-(PYRROLIDIN-1-YL)ETHYL)-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-(R)-OXIDE

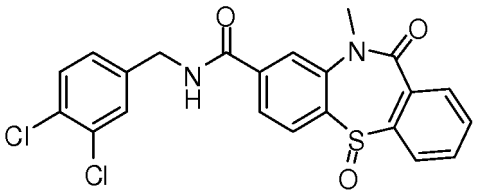
[0346]



[0347] Separation of enantiomers via chiral HPLC: Analytical analysis was performed on a CHIRALPAK®IA® column (4.6 × 250 mm, 5 micron). The mobile phase was 60% of ethanol in hexanes at a flow rate of 1.0 mL/min with a run time of 15 minutes. The sample was detected with a diode array detector (DAD) at 220 nm and 254 nm. Optical rotation was determined with an in-line polarimeter (PDR-Chiral). The first eluting peak: RT = 7.39 minutes; positive optical rotation. The second eluting peak: RT = 11.48 minutes; negative optical rotation. Preparative separation was performed on a CHIRALPAK®IA® column (5× 50 cm, 20 micron). The mobile phase was 60% of ethanol in hexanes at a flow rate of 35 mL/min with. Fraction collection was triggered by UV absorbance (254 nm). LCMS RT = 3.35 min, m/z 398.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{21}H_{24}N_3O_3S$ [M+H$^+$] 398.1533, found 398.1538.

EXAMPLE 123. N-(3,4-DICHLOROBENZYL)-10-METHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

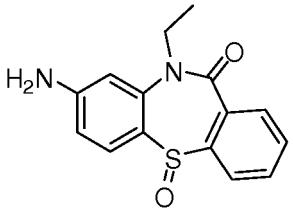
[0348]



[0349] The title compound was prepared according to the general protocol B. LCMS RT = 5.80 min, m/z 459.0 [M+H$^+$].

EXAMPLE 124. 8-AMINO-10-ETHYLDIBENZO[B,F][1,4]THIAZEPIN-11(10H)-ONE 5-OXIDE

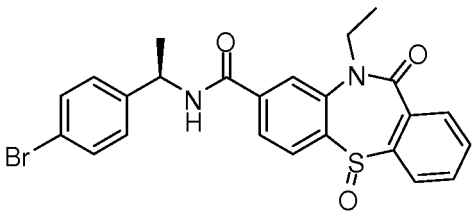
[0350]



[0351] A mixture of 10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxylic acid 5-oxide (73.0 mg, 0.23 mmol), diphenylphosphinyl azide (67.6 mg, 0.28 mmol), TEA (0.048 mL, 0.35 mmol) in dioxane (1.25 mL) was stirred at room temperature for 1 h. Water (1.04 mL, 57.9 mmol) was then added to the solution and the reaction mixture was heated at 80 °C for 4 h. The crude material was partitioned between EtOAc and saturated aqueous $NaHCO_3$ solution. The organic layer was washed with saturated brine, dried over $MgSO_4$, and concentrated under reduced pressure to give the crude title compound as a off-white foam which was used directly in the next reaction without further purification.

EXAMPLE 125. (R)-N-(1-(4-BROMOPHENYL)ETHYL)-10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

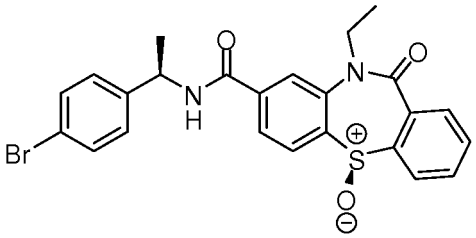
[0352]



[0353] A solution of 10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxylic acid 5-oxide (400 mg, 1.27 mmol) in DMF (12.0 mL) was treated at room temperature with HATU (965 mg, 2.54 mmol) and DIPEA (0.67 mL, 3.81 mmol). After stirring at room temperature for 5 min, (R)-1-(4-bromophenyl)ethanamine (508 mg, 2.54 mmol) was added to the solution . The reaction mixture was stirred at room temperature for an additional 4 h. The mixture was poured into cold HCl solution to induce the precipitation. The precipitation was filtered, washed with water and dried to give 560 mg (89%) of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.93 (d, J=7.8 Hz, 0.5 H), 8.92 (d, J=7.8 Hz, 0.5 H), 7.97 - 8.04 (m, 1 H), 7.91 (td, J=7.8, 1.6 Hz, 1 H), 7.66 - 7.74 (m, 3 H), 7.60 - 7.66 (m, 1 H), 7.55 (tt, J=7.4, 1.2 Hz, 1 H), 7.43 - 7.51 (m, 2 H), 7.25 - 7.34 (m, 2 H), 5.07 (qd, J=7.3, 7.0 Hz, 1 H), 4.49 - 4.67 (m, 1 H), 3.65 - 3.87 (m, 1 H), 1.43 (d, J=7.0 Hz, 1.5 H), 1.41 (d, J=7.0 Hz, 1.5 H), 1.18 (t, J=7.2 Hz, 1.5 H), 1.18 (t, J=7.2 Hz, 1.5 H); LCMS RT = 6.02 min, m/z 497.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{24}H_{22}BrN_2O_3S$ [M+H$^+$] 497.0529, found 497.0526.

EXAMPLE 126. (R)-N-(1-(4-BROMOPHENYL)ETHYL)-10-ETHYL-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-(R)-OXIDE

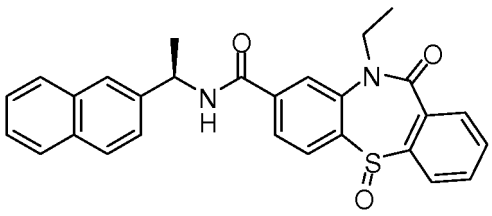
[0354]



[0355] Separation of enantiomers via chiral HPLC: Analytical analysis was performed on a CHIRALPAK®IA® column (4.6 $\times$ 250 mm, 5 micron). The mobile phase was 60% of ethanol in hexanes at a flow rate of 1.0 mL/min with a run time of 15 minutes. The sample was detected with a diode array detector (DAD) at 220 nm and 254 nm. Optical rotation was determined with an in-line polarimeter (PDR-Chiral). The first eluting peak: RT = 5.36 minutes; positive optical rotation. The second eluting peak: RT = 6.44 minutes; negative optical rotation. Preparative separation was performed on a CHIRALPAK®IA® column (5$\times$ 50 cm, 20 micron). The mobile phase was 60% of ethanol in hexanes at a flow rate of 35 mL/min. Fraction collection was triggered by UV absorbance (254 nm). The absolute configuration was assigned by X-ray diffraction. LCMS RT = 6.02 min, m/z 497.0 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{24}H_{22}BrN_2O_3S$ [M+H$^+$] 497.0529, found 497.0536.

EXAMPLE 127. (R)-10-ETHYL-N-(1-(NAPHTHALEN-2-YL)ETHYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-OXIDE

[0356]

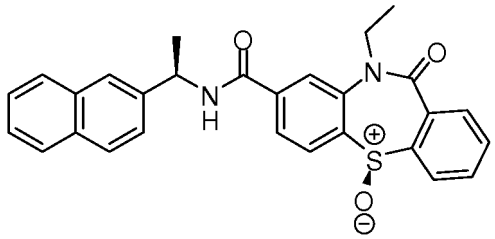


[0357] A solution of 10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxylic acid 5-oxide (400 mg, 1.27 mmol) in DMF (12.0 mL) was treated at room temperature with HATU (965 mg, 2.54 mmol) and DIPEA (0.67 mL, 3.81

mmol). After stirring at room temperature for 5 min, (R)-1-(naphthalen-2-yl)ethanamine (434 mg, 2.54 mmol) was added to the solution . The reaction mixture was stirred at room temperature for an additional 4 h. The mixture was poured into cold HCl solution to induce the precipitation. The precipitation was filtered, washed with water and dried to give 464 mg (78%) of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.05 (d, J=7.4 Hz, 1 H), 8.06 (dd, J=9.0, 1.6 Hz, 1 H), 7.92 - 8.01 (m, 1 H), 7.80 - 7.91 (m, 4 H), 7.63 - 7.77 (m, 4 H), 7.52 - 7.62 (m, 2 H), 7.43 - 7.52 (m, 2 H), 5.20 - 5.40 (m, 1 H), 4.52 - 4.70 (m, 1 H), 3.78 (dq, J=13.9, 6.8 Hz, 1 H), 1.57 (d, J=6.8 Hz, 1.5 H), 1.56 (d, J=6.8 Hz, 3 H), 1.21 (t, J=7.0 Hz, 1.5 H), 1.20 (t, J=7.0 Hz, 1.5 H); LCMS RT = 6.08 min, m/z 469.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{28}H_{25}N_2O_3S$ [M+H$^+$] 469.1580, found 469.1580.

EXAMPLE 128. (R)-10-ETHYL-N-(1-(NAPHTHALEN-2-YL)ETHYL)-11-OXO-10,11-DIHYDRODIBENZO[B,F][1,4]THIAZEPINE-8-CARBOXAMIDE 5-(R)-OXIDE

[0358]

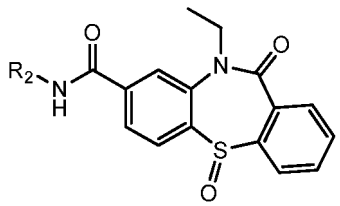


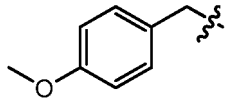
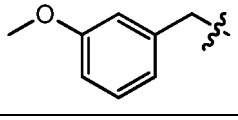
[0359] Separation of enantiomers via chiral HPLC: Analytical analysis was performed on a CHIRALPAK®IA® column (4.6 $\times$ 250 mm, 5 micron). The mobile phase was 60% of ethanol in hexanes at a flow rate of 1.0 mL/min with a run time of 15 minutes. The sample was detected with a diode array detector (DAD) at 220 nm and 254 nm. Optical rotation was determined with an in-line polarimeter (PDR-Chiral). The first eluting peak: RT = 5.84 minutes; positive optical rotation. The second eluting peak: RT = 7.19 minutes; negative optical rotation. Preparative separation was performed on a CHIRALPAK®IA® column (5$\times$ 50 cm, 20 micron). The mobile phase was 60% of ethanol in hexanes at a flow rate of 35 mL/min. Fraction collection was triggered by UV absorbance (254 nm). LCMS RT = 6.08 min, m/z 469.1 [M+H$^+$]; HRMS (ESI) m/z calcd for $C_{28}H_{25}N_2O_3S$ [M+H$^+$] 469.1580, found 469.1579.

EXAMPLE 129. ADDITIONAL DOPAMINE D_2 SELECTIVE COMPOUNDS

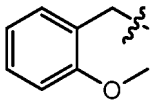
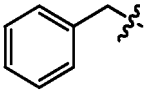
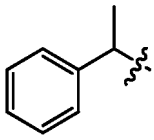
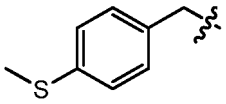
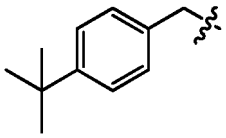
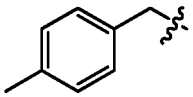
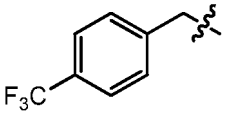
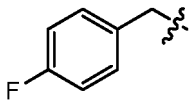
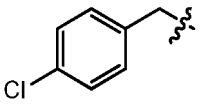
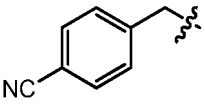
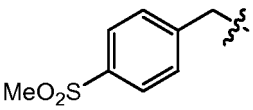
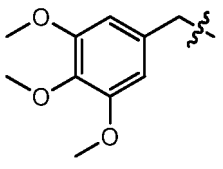
[0360] The compounds shown in Tables 6 to 11 were prepared by the synthetic method of Example 6. Those of skill in the art will recognize routine changes in reactants and reaction conditions needed to produce each particular compound. Compounds were tested in the dopamine D_2 calcium release assay provided in Example 1. All compounds shown in Table 6 exhibited an AC_{50} of less than 10 micromolar in assay. Those indicated with an asterisk, *, exhibited an AC_{50} of less than 1 micromolar in the dopamine D_2 calcium release assay.

TABLE 6 - Additional Dopamine D_2 Selective Compounds



Cmp. No.	R_2	Ca^{2+} AC_{50}
1		*
2		*

(continued)

Cmp. No.	R_2	Ca^{2+} AC_{50}
3		
4		*
5		*
6		*
7		*
8		*
9		*
10		*
11		*
12		*
13		*
14		

(continued)

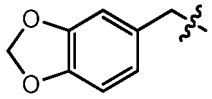
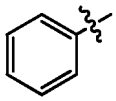
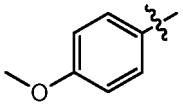
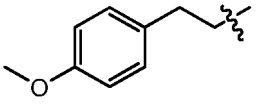
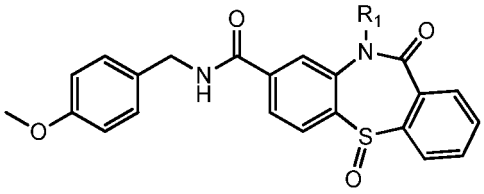
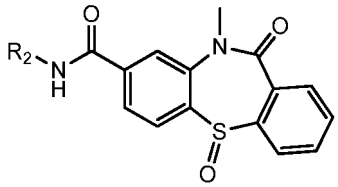
Cmp. No.	R_2	Ca^{2+} AC_{50}
15		*
16		*
17		*
18		*

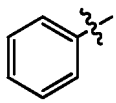
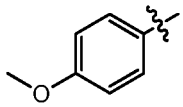
TABLE 7 - Additional Dopamine D_2 Selective Compounds



Cmp. No.	R_1	Ca^{2+} AC_{50}
19	H	
20	Methyl	*
21	n-Propyl	*
22	Benzyl	

TABLE 8 - Additional Dopamine D_2 Selective Compounds



Cmp. No.	R_2	Ca^{2+} AC_{50}
23		
24		*

(continued)

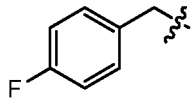
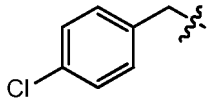
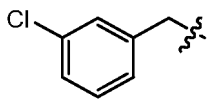
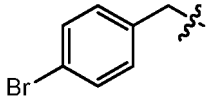
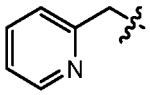
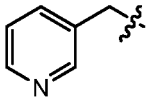
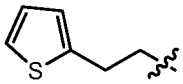
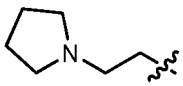
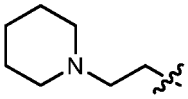
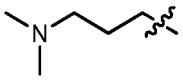
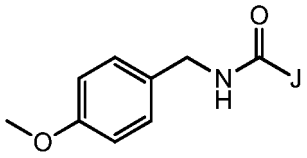
Cmp. No.	R_2	Ca^{2+} AC_{50}
25	Benzyl	*
26		*
27		*
28		*
29		*
30		
31		*
32		*
33		*
34		*
35		*

TABLE 9 - Additional Dopamine D_2 Selective Compounds



(continued)

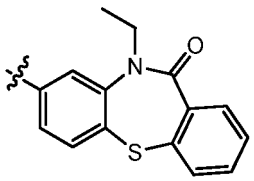
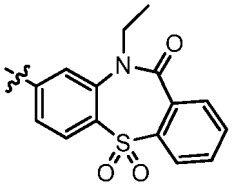
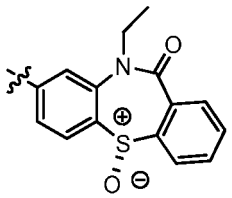
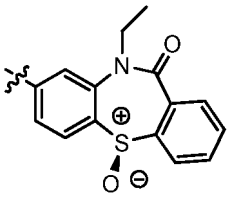
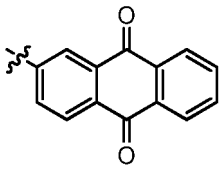
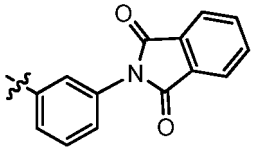
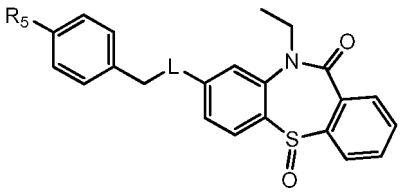
Cmp. No.	J	Ca^{2+} AC_{50}
36		*
37		
38		*
39		
40		
41		

TABLE 10 - Additional Dopamine D_2 Selective Compounds



(continued)

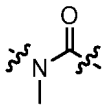
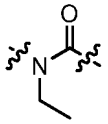
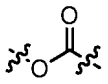
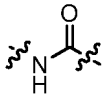
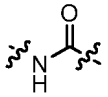
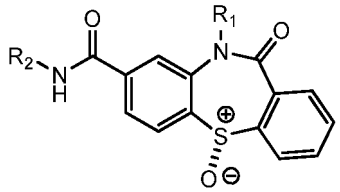
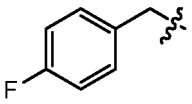
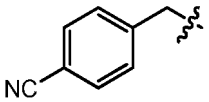
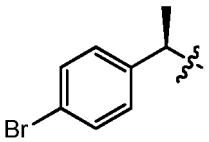
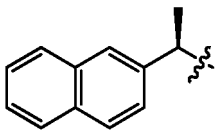
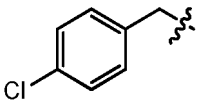
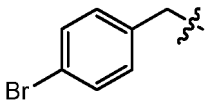
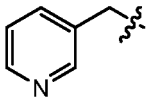
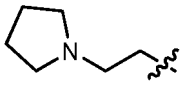
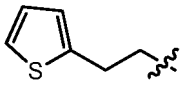
Cmp. No.	R_5	L	Ca^{2+} AC_{50}
42	Methoxy		
43	H		
44	Methoxy		
45	Methoxy		*
46	F		*

TABLE 11 - Additional Dopamine D_2 Selective Compounds



Cmp. No.	R_1	R_2	Ca^{2+} AC_{50}
47	Ethyl		*
48	Ethyl		*
49	Ethyl		*
50	Ethyl		*
51	Methyl		*

(continued)

Cmp. No.	R_1	R_2	Ca^{2+} AC_{50}
52	Methyl		*
53	Methyl		*
54	Methyl		*
55	Methyl		*

EXAMPLE 130. SELECTIVE ACTIVITY OF COMPOUNDS

[0361] Certain compounds were tested in the D_2 beta arrestin assay of Example 2, the D_3 beta arrestin assay of Example 4, the D_2 binding assay of Example 3, the D_3 binding assay of Example 5. The ratio of D_3/D_2 activity in the beta arrestin and binding assay were calculated to determine compound activity.

TABLE 12 - Selectivity Data

Compound No.	D_3/D_2 beta-arrestin IC_{50} ratio	D_3/D_2 binding K_i ratio
1	2.0	6.0
32	22.3	28.7
38	2.5	N/A
47	5.6	2.6
48	6.3	5.7
49	7.1	1.3
50	11.2	16.2
51	4.5	N/A
52	4.6	1.5
53	5.0	70.0
54	7.2	1.7
R-55	N/A	N/A
55	17.8	29.0

[0362] Graphical representation of the beta-arrestin and radioligand binding assay data in Table 12 for compounds 1 and 55 can be seen in Figures 1 and 2.

[0363] The above data show that this series of compounds can achieve significant potency/affinity separation from the D_3 dopamine receptor, which is a highly novel finding that may have therapeutic impact. Because all FDA approved drugs that target the D_2 receptor, particularly those that antagonize the receptor, such as antipsychotics, exhibit cross GPCR reactivity, a fact that may contribute to their well-known side effects, it was of interest to profile one compound against a panel of GPCRs. Table 13 shows an affinity profile of compound 55 against a panel of 46 GPCRs and related proteins. Antipsychotic drugs (depending on the specific drug) typically interact with a range of serotonergic, adrenergic, histaminergic, and muscarinic receptors. In contrast, compound 55 was found to bind with significant affinity (inhibition

of binding >50%) to only two serotonin receptors and the D_2 and D_3 receptors. Notably, the affinity for the two serotonin receptors was similar to that for the D_3 receptor, indicating compound 55 is very highly selective for the D_2 receptor.

TABLE 13

Receptor	Inhibition (%)	Receptor	Inhibition (%)	Receptor	Inhibition (%)
5-HT1A	8.2	Beta1	12.6	H1	41.6
5-HT1B	24.0	Beta2	-13.2	H2	-9.2
5-HT1D	13.1	Beta3	6.6	H3	-23.6
5-HT1E	9.9	BZP Rat Brain Site	0.5	H4	TBD
5-HT2A	46.3	GABAA	10.6	KOR	18.2
5-HT2B	40.1	D1	-6.8	M1	-0.6
5-HT2C	64.5	D2	92.3	M2	-1.7
5-HT3	8.5	D3	59.1	M3	5.2
5-HT4	TBD	D4	32.2	M4	2.4
5-HT5A	9.5	D5	-8.5	M5	-6.5
5-HT6	-15.6	DAT	-5.3	MOR	5.7
5-HT7	53.3	DOR	-23.6	NET	8.9
Alpha1A	-13.4			PBR	31
Alpha1B	-0.2			SERT	4.8
Alpha1D	-22.6			Sigma 1	17.5
Alpha2A	7.3			Sigma 2	-16.5
Alpha2B	31.2				
Alpha2C	20.9				

EXAMPLE 131. PET STUDY, DISPLACEMENT OF THE D2 RECEPTOR LABEL [^{11}C]SV-130 WITH A COMPOUND OF FORMULA I

[0364] Positron emission tomography (PET) was performed using live monkeys. A radioactive PET probe ([^{11}C]SV-130) for the D2 receptor was injected intravenously. PET images of coronal sections of the brain were obtained at the level of the caudate putamen. In the baseline imaging section, the PET probe showed high uptake in the caudate putamen, with areas of high D2 receptor expression appearing orange-red in the baseline images. Monkeys were treated (i.v.) with either 1 mg/kg or 5 mg/kg ML321, a compound of Formula I (compound 55, Example 61).

[0365] Summed MicroPET coronal images of the caudate putamen taken from 20 to 100 minutes post ML321 injection showed that ML321 blocks the binding of the D2 recepor PET probe in the caudate putamen in a dose-dependent

fashion. The 5 mg/kg dose almost completely blocked the ([^{11}C]SV-130) labeling.

[0366] The time course of PET ([^{11}C]SV-130) labelling of the caudate, putamen, and cerebellumum in the absence or presence of either 1 mg/kg or 5 mg/kg ML321 was plotted. In both the caudate and putamen the graphs showed uptake of [^{11}C]SV-130 and a continued strong signal from the labelled probe over the 100 minute period plotted. When ML321 was injected i.v. the [^{11}C]SV-130 signal decreased gradually from about 20 minutes through the 100 minute observation period. The [^{11}C]SV-130 signal decrease was particularly dose dependent in the putamen graph. The cerebellum graph was used as a negative control as this brain region lacks D2 receptors and exhibits only non-specific uptake of the probe.

[0367] The significance of the PET [^{11}C]SV-130 labelling data are two-fold. First the experiments provide direct evidence that ML321 can cross the blood-brain barrier in primates and interact with regions of the brain containing high levels of D2 receptors. Second, the experiments provide direct evidence that ML321 can occupy D2 receptors in the CNS in living animals and completely block D2 receptors at a reasonable pharmacological dose.

EXAMPLE 132. BEHAVIORIAL EFFECTS OF A COMPOUND OF FORMULA I

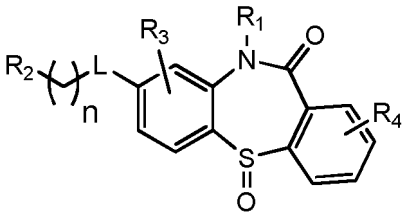
[0368] These experiments test the ability of a compound of Formula I, ML321, to affect physiological or behavioral responses in rats that are mediated by D2 or D3 receptors. Sumanirole, an agonist of the D2 receptor, produces hypothermia in rats when administered subcutaneously. This response is known to be mediated by the D2 receptor and not the D3 receptor (Collins et al., Psychopharmacology (Berl). 2007, 193(2): 159-70). ML321 was found to significantly and dose-dependently block the sumanirole-induced hypothermia response when administered subcutaneously at doses of 3.2 and 10 mg/kg. The response was completely blocked at 10 mg/kg.

[0369] Pramipexole, an agonist of the D3 receptor, produces yawning when administered subcutaneously. This response is known to be mediated by the D3 receptor and not the D2 receptor (Collins, *Id.*). ML321 was found to have no effect on pramipexole-induced yawning using the same doses that blocked the hypothermia response (3.2 and 10 mg/kg). Observations of the pramipexole-induced yawning over an extended time period in the presence or absence of ML321 confirmed that ML321 had no effect on pramipexole-induced yawning.

[0370] The sumanirole-induced hypothermia and pramipexole-induced yawning experiments show ML321 can act selectively to block the D2 receptor without blocking the D3 receptor when administered to living animals. Thus, the D2 selectivity identified using cellular assays can also be seen in living animals.

Claims

1. A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein

L is -NHC(O)-, -C(O)NH-, -OC(O)- or -C(O)O-;
n is and integer from 1 to 4 and

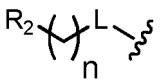
is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_2haloalkyl, or C_1-C_2haloalkoxy;
R_1 is hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, (C_3-C_7cycloalkyl)C_0-C_2alkyl, (mono- or di-C_1-C_4alkylamino)C_1-C_4alkyl, or (mono- or di-C_1-C_4alkylamino)C_1-C_4alkoxy;
R_2 is mono-, bi-, or tricyclic carbocyclic or heterocylic group, a (mono- or di-C_1-C_4alkylamino)C_2-C_4alkyl group, or C_4-C_8alkyl, each of which R_2 is unsubstituted or substituted with one more substituents independently chosen

from halogen, hydroxyl, amino, nitro, cyano, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, $-OR_{11}$, $-(CH_2)_{0-4}C(O)R_{11}$, $-(CH_2)_{0-4}NR_{11}R_{12}$, $-(CH_2)_{0-4}C(O)NR_{11}R_{12}$, $-(CH_2)_{0-4}N(R_{11})C(O)(R_{12})$, $-(CH_2)_{0-4}C(O)OR_{11}$, $-(CH_2)_{0-4}OC(O)R_{11}$, $-(CH_2)_{0-4}C(S)R_{11}$, $-(CH_2)_{0-4}S(O)_aR_{11}$, $-(CH_2)_{0-4}S(O)_bNR_{11}R_{12}$, $-(CH_2)_{0-4}N(R_{11})S(O)_bR_{12}$, and (phenyl)$C_0$-$C_2$alkyl, where a is 0, 1, or 2, and b is 1 or 2,

R_{11}, R_{12}, and R_{13} are independently chosen at each occurrence from hydrogen and a C_1-C_6aliphatic group; each of R_{11}, R_{12}, and R_{13} is unsubstituted or substituted with one or more substituents independently chosen from: halogen, hydroxyl, vinyl, allenyl, oxo, cyano, amino, -COOH, C_1-C_6alkyl, C_1-C_6alkoxy, (mono- and di-C_1-C_6alkylamino)C_0-C_2alkyl, C_1-C_6alkylester, C_1-C_6alkylthio, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy;

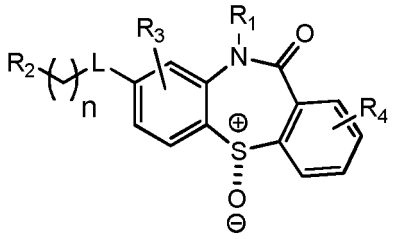
R_3 and R_4 are 0 or 1 or more substituents independently chosen from halogen, hydroxyl, amino, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkanoyl, (mono- and di-C_1-C_4alkylamino)C_0-C_2alkyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy;

with the proviso that when R_1 is ethyl, the group



is not 4-methoxybenzyl-NHC(O)-, pyridin-2-ylmethyl-NHC(O)-, 3-(morpholin-1-yl)propyl-NHC(O)-, 3-(azepan-1-yl)propyl-NHC(O)-, 3-(azepan-1-yl)ethyl-NHC(O)-, 3-(pyrrolidin-1-yl)propyl-NHC(O)-, 3-(4-methylpiperazin-1-yl)propyl-NHC(O)-, 3-(piperidin-1-yl)propyl-NHC(O)-, di-isopropylaminopropyl-NHC(O)-, di-propylaminopropyl-NHC(O)-, di-butylaminopropyl-NHC(O)-, or 3-(butyl(ethyl)amino)propyl-NHC(O)-.

2. A compound or salt of Claim 1, of the formula



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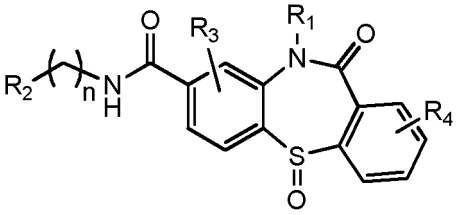
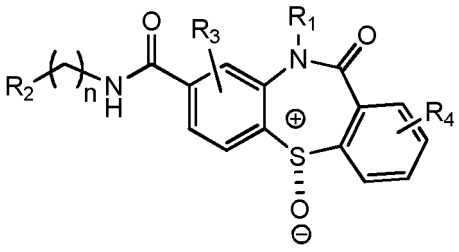
3. A compound or salt of Claim 1, of the formula



or



.

4. A compound or salt of any one of Claims 1 to 3, wherein
R_1 is C_1-C_6alkyl, C_2-C_6alkenyl, or (C_3-C_7cycloalkyl)C_0-C_2alkyl, preferably C_1-C_6alkyl.

5. A compound or salt of any one of Claims 1 to 4, wherein
R_1 is methyl or ethyl, and R_3 and R_4 are both 0 substituents.

6. A compound or salt of any one of Claims 1 to 4, wherein
R_3 and R_4 are both 0, 1, or 2 substituents independently chosen from halogen, hydroxyl, amino, cyano, C_1-C_2alkyl, C_1-C_2alkoxy, trifluoromethyl, difluoromethoxy, and trifluoromethoxy.

7. A compound or salt of any one of Claims 1 to 6, wherein n is 1, 2, or 3 and

is unsubstituted or substituted with one C_1-C_4alkyl substituent or one trifluoromethyl substituent.

8. A compound or salt of Claim 7, wherin n is 1 or 2 and

is unsubstituted or substituted with one methyl substituent.

9. A compound or salt of any one of Claims 1 to 8, wherein
R_2 is C_3-C_7cycloalkyl, 5- or 6-membered heterocycloalkyl containing 1 or 2 heteroatoms selected from N, O, or S, phenyl, naphthyl, phenyl fused to a 5- or 6-membered heterocyclic ring containing 1 or 2 oxygen atoms, pyridyl, pyrimidinyl, pyrazinyl, thienyl, furanyl, pyrrolyl, thiazolyl, indolyl, or imidazolyl, each of which R_2 is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, (mono- and di-C_1-C_4alkylamino)C_0-C_2alkyl, C_1-C_4alkylthio, C_1-C_4alkylsulfonyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

10. A compound or salt of Claim 9, wherein
R_2 is phenyl, naphthyl, benzo[d][1,3]dioxolyl, pyridyl, thienyl, furanyl, indolyl, imidazolyl, thiazolyl, pyrrolidinyl, piperidinyl, piperazinyl, pyrrolyl, morpholinyl, each which is substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, (mono- and di-C_1-C_4alkylamino)C_0-C_2alkyl, C_1-C_4alkylthio, C_1-C_4alkylsulfonyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

11. A compound or salt of Claim 9, wherein
R_2 is phenyl, naphthyl, benzo[d][1,3]dioxolyl, pyridyl, thienyl, pyrrolidinyl, piperidinyl, piperazinyl, each which is substituted with one or more substituents independently chosen from halogen, hydroxyl, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, methylthio, methylsulfonyl, trifluoromethyl, and trifluoromethoxy.

12. A compound or salt of Claim 3, wherein
R_1 is C_1-C_6alkyl or (C_3-C_7cycloalkyl)C_0-C_2alkyl;
R_3 and R_4 and both 0, 1, or 2 substituents independently chosen from halogen, hydroxyl, amino, cyano, C_1-C_2alkyl, C_1-C_2alkoxy, trifluoromethyl, difluoromethoxy, and trifluoromethoxy;
n is 1, 2, or 3 and

is unsubstituted or substituted with one C_1-C_4alkyl substituent or one trifluoromethyl substituent; and
R_2 is phenyl, naphthyl, benzo[d][1,3]dioxolyl, pyridyl, thienyl, furanyl, indolyl, imidazolyl, thiazolyl, pyrrolidinyl, piperidinyl, piperazinyl, pyrrolyl, morpholinyl, each which is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, (mono- and di-C_1-C_4alkylamino)C_0-C_2alkyl, C_1-C_4alkylthio, C_1-C_4alkylsulfonyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy;
R_2 is thienyl, which is unsubstituted or substituted with one or more substituents independently chosen from halogen, C_1-C_2alkyl, or C_1-C_2alkoxy; or
R_2 is phenyl which is unsubstituted or substituted with one or more substituents independently chosen from halogen, hydroxyl, amino, cyano, C_1-C_4alkyl, C_1-C_4alkoxy, (mono- and di-C_1-C_4alkylamino)C_0-C_2alkyl, C_1-C_4alkylthio, C_1-C_4alkylsulfonyl, C_1-C_2haloalkyl, and C_1-C_2haloalkoxy.

13. A compound or salt thereof of Claim 1, wherein the compound is

10-Ethyl-*N*-(3-methoxybenzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-*N*-(2-methoxybenzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-Benzyl-10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide; 10-Ethyl-11-oxo-*N*-(1-phenylethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;

10-Ethyl-*N*-(4-(methylthio)benzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-(4-tert-Butylbenzyl)-10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-*N*-(4-methylbenzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-11-oxo-*N*-(4-(trifluoromethyl)benzyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-N-(4-fluorobenzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-(4-Cyanobenzyl)-10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-N-(4-(methylsulfonyl)benzyl)-11-oxo-10,11-ihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-11-oxo-N-(3,4,5-trimethoxybenzyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-(benzo[d][1,3]dioxol-5-ylmethyl)-10-ethyl-11-oxo-10,11dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-N-(4-methoxyphenethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-(4-Methoxybenzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-(4-Methoxybenzyl)-10-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-(4-Methoxybenzyl)-11-oxo-10-propyl-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-Benzyl-10-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-(4-Fluorobenzyl)-10-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-(4-Chlorobenzyl)-10-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-(3-Chlorobenzyl)-10-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-(4-Bromobenzyl)-10-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Methyl-11-oxo-N-(pyridin-2-ylmethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Methyl-11-oxo-N-(pyridin-3-ylmethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Methyl-11-oxo-N-(2-(thiophen-2-yl)ethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Methyl-11-oxo-N-(2-(pyrrolidin-1-yl)ethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Methyl-11-oxo-N-(2-(piperidin-1-yl)ethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-(3-(Dimethylamino)propyl)-10-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-N-(4-methoxybenzyl)-N-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-Benzyl-N,10-diethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-(4-methoxybenzyl)carboxylate 5-oxide;
N-(10-Ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepin-8-yl)-2-(4-methoxyphenyl)acetamide 5-oxide;
N-(10-Ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepin-8-yl)-2-(4-fluorophenyl)acetamide 5-oxide;
10-Ethyl-N-(4-fluorobenzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-(S)-oxide;
N-(4-Cyanobenzyl)-10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-(S)-oxide;
(R)-N-(1-(4-Bromophenyl)ethyl)-10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-(S)-oxide;
(R)-10-Ethyl-N-(1-(naphthalen-2-yl)ethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-(S)-oxide;
N-(4-Chlorobenzyl)-10-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-(S)-oxide;
N-(4-Bromobenzyl)-10-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-(S)-oxide;
10-Methyl-11-oxo-N-(pyridin-3-ylmethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-(S)-oxide;
10-Methyl-11-oxo-N-(2-(pyrrolidin-1-yl)ethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-(S)-oxide;
10-Ethyl-11-oxo-N-(2-(thiophen-2-yl)ethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Methyl-11-oxo-N-(2-(thiophen-2-yl)ethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-(S)-oxide;
N-(4-Methoxybenzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide;
10-Ethyl-11-oxo-N-(3-(trifluoromethyl)benzyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-N-(3-methylbenzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-(3-Chlorobenzyl)-10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-(Biphenyl-3-ylmethyl)-10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-11-oxo-N-(3-phenylpropyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-(2,3-Dimethoxybenzyl)-10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-11-oxo-N-(thiophen-2-ylmethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8 - carboxamide 5-oxide;
10-Ethyl-N-(furan-2-ylmethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;

10-Ethyl-N-((4-methylthiophen-2-yl)methyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-N-(2-morpholinoethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-N-((1-methylpiperidin-4-yl)methyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-(2-Chlorobenzyl)-10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-11-oxo-N-(2-(trifluoromethyl)benzyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-N-(2-methylbenzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-(2,5-Dimethoxybenzyl)-10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-((1H-Indol-6-yl)methyl)-10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-(2,4-Dimethoxybenzyl)-10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-(4-Cyanobenzyl)-10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-(R)-oxide;
N-(2,6-Dimethoxybenzyl)-10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-N-(4-fluorobenzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-(R)-oxide;
10-Ethyl-N-(4-methylphenethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-11-oxo-N-(4-phenylbutyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-N-(2-(furan-2-yl)propyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-((1H-Imidazol-2-yl)methyl)-10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-N-(2-(2-methylthiazol-4-yl)ethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-N-(3-methoxyphenethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-N-((1-methyl-1H-imidazol-5-yl)methyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-N-((2-methylthiazol-4-yl)methyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-N-((1-methyl-1H-imidazol-4-yl)methyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-N-(3-fluorobenzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-(3-(Dimethylamino)propyl)-10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-(4-Aminophenethyl)-10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-(4-Methoxybenzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5,5-dioxide;
N-(4-Chlorobenzyl)-10-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-(R)-oxide;
N-(4-Bromobenzyl)-10-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-(R)-oxide;
N-(4-Iodobenzyl)-10-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-(3-Fluorobenzyl)-10-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Methyl-11-oxo-N-(2-(thiophen-2-yl)ethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-(R)-oxide;
(S)-10-Methyl-11-oxo-N-(1-phenylethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
N-(3,5-Difluorobenzyl)-10-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Methyl-11-oxo-N-(pyridin-3-ylmethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-(R)-oxide;
N-(4-(Dimethylamino)butyl)-10-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
(R)-10-Methyl-11-oxo-N-(1-phenylethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
(S)-N-(1-(4-Chlorophenyl)ethyl)-10-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
(R)-N-(1-(4-Chlorophenyl)ethyl)-10-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Methyl-11-oxo-N-(3-(piperidin-1-yl)propyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Methyl-11-oxo-N-(2,2,2-trifluoro-1-phenylethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Ethyl-11-oxo-N-(2,2,2-trifluoro-1-phenylethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
10-Methyl-11-oxo-N-(2-(pyrrolidin-1-yl)ethyl)-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-(R)-oxide;

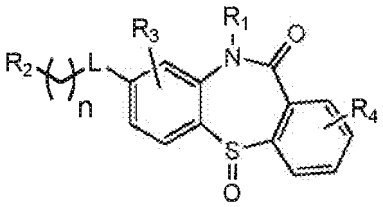
N-(3,4-Dichlorobenzyl)-10-methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
(R)-N-(1-(4-Bromophenyl)ethyl)-10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
(R)-N-(1-(4-Bromophenyl)ethyl)-10-ethyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-(R)-oxide;
(R)-10-Ethyl-N-(1-(naphthalen-2-yl)ethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-oxide;
(R)-10-Ethyl-N-(1-(naphthalen-2-yl)ethyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5-(R)-oxide; or
10-ethyl-N-(4-methoxybenzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazepine-8-carboxamide 5,5-dioxide.

14. A pharmaceutical composition comprising a compound or salt of any one of Claims 1to 13 and a pharmaceutically acceptable carrier.

15. The compound or salt of any one of Claims 1 to 13, for use in the treatment of Tourette's syndrome, bipolar disorder, hyperprolactinemia, psychosis, depression, Huntington's chorea, or schizophrenia.

Patentansprüche

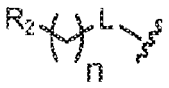
1. Zusammensetzung der Formel:



oder ein pharmazeutisch zulässiges Salz davon, wobei L -NHC(O)-, -C(O)NH-, -OC(O)- oder -C(O)O- ist;
n eine ganze Zahl von 1 bis 4 ist und

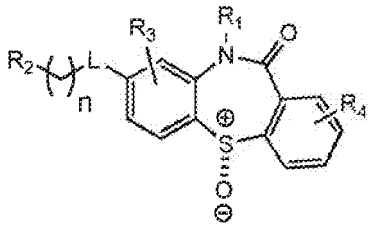
unsubstituiert oder mit einem oder mehreren Substituenten substituiert ist, die unabhängig voneinander unter Halogen, Hydroxyl, Amino, Cyano, C_1-C_4Alkyl, C_1-C_4Alkoxy, C_1-C_2Haloalkyl oder C_1-C_2Haloalkoxy ausgewählt sind;
R_1 Wasserstoff, C_1-C_6Alkyl, C_2-C_6Alkenyl, (C_3-C_7Cycloalkyl) C_0-C_2Alkyl, (mono- oder di-C_1-C_4Alkylamino)C_1-C_4Alkyl, oder (mono- oder di-C_1-C_4Alkylamino)C_1-C_4Alkoxy ist;
R_2 eine mono-, bi- oder trizyklische carbozyklische oder heterozyklische Gruppe, eine (mono- oder di-C_1-C_4Alkylamino)C_2-C_4Alkylgruppe oder C_4-C_8Alkyl ist, von denen jede R_2 unsubstituiert oder mit einem weiteren Substituenten substituiert ist, der unabhängig unter Halogen, Hydroxyl, Amino, Nitro, Cyano, C_1-C_6Alkyl, C_2-C_6Alkenyl, C_2-C_6Alkynyl, $-OR_{11}$, $-(CH_2)_{0-4}C(0)R_{11}$, $-(CH_2)_{0-4}NR_{11}R_{12}$,$-(CH2)_{0-4}C(O)NR_{11}R_{12}$, $-(CH_2)_{0-4}N(R_{11})C(0)R_{12})$, $-(CH_2)_{0-4}C(0)OR_{11}$, $-(CH_2)_{0-4}OC(0)R_{11}$, $-(CH_2)_{0-4}C(S)R_{11}$, $-(CH_2)_{0-4}S(O)_aR_{11}$, $-(CH_2)_{0-4}S(O)_bNR_{11}R_{12}$,$-(CH_2)_{0-4}N(R_{11})S(O)_bR_{12}$ und (Phenyl) C_0-C_2Alkyl ausgewählt ist, wobei a 0, 1, oder 2 ist, und b 1 oder 2 ist,
R_{11}, R_{12} und R_{13} unabhängig bei jedem Auftreten unter Wasserstoff und einer C_1-C_6aliphatischen Gruppe ausgewählt sind;
jedes von R_{11}, R_{12} und R_{13} unsubstituiert oder mit einem oder mehreren Substituenten substituiert ist, die unabhängig ausgewählt sind unter: Halogen, Hydroxyl, Vinyl, Allenyl, Oxo, Cyano, Amino, -COOH, C_1-C_6Alkyl, C_1-C_6Alkoxy, (mono- und di-C_1-C_6Alkylamino)C_0-C_2Alkyl, C_1-C_6Alkylester, C_1-C_6Alkylthio, C_1-C_2Haloalkyl und C_1-C_2Haloalkoxy;
R_3 und R_4 0 oder 1 oder mehr Substituenten sind, die unabhängig unter Halogen, Hydroxyl, Amino, Cyano, C_1-C_4Alkyl, C_1-C_4Alkoxy, C_2-C_4Alkanoyl, (mono- und di-C_1-C_4Alkylamino)C_0-C_2Alkyl, C_1-C_2Haloalkyl und C_1-C_2Haloalkoxy ausgewählt sind;

mit der Maßgabe, dass, wenn R_1 Ethyl ist, die Gruppe

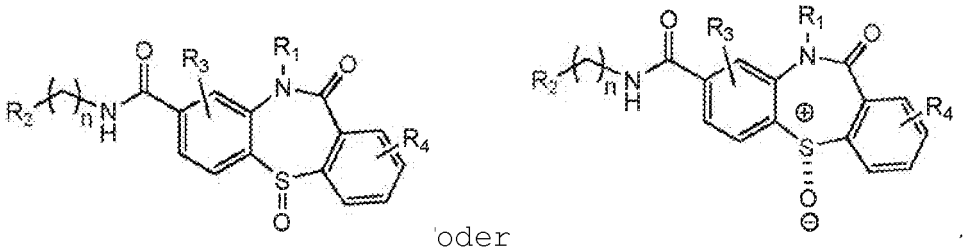


nicht 4-Methoxybenzyl-NHC(O)-, Pyridin-2-ylmethyl-NHC(O)-, 3-(Morpholin-1-yl)Propyl-NHC(O)-, 3-(Azepan-1-yl)Propyl-NHC(O)-, 3-(Azepan-1-yl)Ethyl-NHC(O)-, 3-(Pyrrolidin-1-yl)Propyl-NHC(O)-, 3-(4-Methylpiperazin-1-yl)propyl-NHC(O)-, 3-(Piperidin-1-yl)propyl-NHC(O)-, di-isopropylaminopropyl-NHC(O)-, di-propylaminopropyl-NHC(O)-, di-butylaminopropyl-NHC(O)- oder 3-(Butyl(ethyl)amino)propyl-NHC(O)- ist.

2. Verbindung oder Salz nach Anspruch 1 der Formel



3. Verbindung oder Salz nach Anspruch 1 der Formel



oder

4. Verbindung oder Salz nach einem beliebigen der vorstehenden Ansprüche 1 bis 3, wobei R_1 C_1-C_6Alkyl, C_2-C_6Alkenyl oder (C_3-C_7Cycloalkyl) C_0-C_2Alkyl, vorzugsweise C_1-C_6Alkyl ist.

5. Verbindung oder Salz nach einem beliebigen der vorstehenden Ansprüche 1 bis 4, wobei R_1 Methyl oder Ethyl ist, und R_3 und R_4 beide 0 Substituenten sind.

6. Verbindung oder Salz nach einem beliebigen der vorstehenden Ansprüche 1 bis 4, wobei R_3 und R_4 jeweils 0, 1 oder 2 Substituenten sind, die unabhängig unter Halogen, Hydroxyl, Amino, Cyano, C_1-C_2Alkyl, C_1-C_2Alkoxy, Trifluoromethyl, Difluoromethoxy und Trifluoromethoxy ausgewählt sind.

7. Verbindung oder Salz nach einem beliebigen der vorstehenden Ansprüche 1 bis 6, wobei n 1, 2 oder 3 ist, und

unsubstituiert oder mit einem C_1-C_4Alkylsubstituenten oder einem Trifluoromethylsubstituenten substituiert ist.

8. Verbindung oder Salz nach Anspruch 7, wobei n 1 oder 2 ist,

unsubstituiert oder mit einem Methylsubstituenten substituiert ist.

9. Verbindung oder Salz nach einem beliebigen der vorstehenden Ansprüche 1 bis 8, wobei
R_2 C3-C_7Cycloalkyl, 5- oder 6-gliedriges Heterocycloalkyl ist, das 1 oder 2 Heteroatome enthält, die unter N, 0 oder S, Phenyl, Naphthyl, Phenyl kondensiert an einen 5- oder 6-gliedrigen heterozyklischen Ring mit 1 oder 2 Sauerstoffatomen Pyridyl, Pyrimidinyl, Pyrazinyl, Thienyl, Furanyl, Pyrrolyl, Thiazolyl, Indolyl oder Imidazolyl ausgewählt sind, von denen jedes R_2 unsubstitutiert oder mit einem oder mehreren Substituenten substituiert ist, die unabhängig unter Halogen, Hhydroxyl, Amino, Cyano, C_1-C_4Alkyl, C_1-C_4Alkoxy, (mono- und di-C_1-C_4Alkylamino)C_0-C_2Alkyl, C_1-C_4Alkylthio, C_1-C_4Alkylsulfonyl, C_1-C_2Haloalkyl und C_1-C_2Haloalkoxy ausgewählt sind.

10. Verbindung oder Salz nach Anspruch 9, wobei
R_2 Phenyl, Naphthyl, Benzo[d][1,3]Dioxolyl, Pyridyl, Thienyl, Furanyl, Indolyl, Imidazolyl, Thiazolyl, Pyrrolidinyl, Piperidinyl, Piperazinyl, Pyrrolyl, Morpholinyl ist, die jeweils mit einem oder mehreren Substituenten substituiert sind, die unabhängig unter Halogen, Hydroxyl, Amino, Cyano, C_1-C_4Alkyl, C_1-C_4Alkoxy, (mono- and di-C_1-C_4Alkylamino)C_0-C_2Alkyl, C_1-C_4Alkylthio, C_1-C_4Alkylsulfonyl, C_1-C_2Haloalkyl und C_1-C_2Haloalkoxy ausgewählt sind.

11. Verbindung oder Salz nach Anspruch 9, wobei
R_2 Phenyl, Naphthyl, Benzo[d][1,3]Dioxolyl, Pyridyl, Thienyl, Pyrrolidinyl, Piperidinyl, Piperazinyl ist, die jeweils mit einem oder mehreren Substituenten substituiert sind, die unabhängig unter Halogen, Hydroxyl, Cyano, C_1-C_4Alkyl, C_1-C_4Alkoxy, Methylthio, Methylsulfonyl, Trifluoromethyl und Trifluoromethoxy ausgewählt sind.

12. Verbindung oder Salz nach Anspruch 3, wobei
R_1 C_1-C_6alkyl oder (C_3-C_7Cycloalkyl)C_0-C_2alkyl ist;
R_3 und R_4 jeweils 0, 1 oder 2 Substituenten sind, die unabhängig unter Halogen, Hydroxyl, Amino, Cyano, C_1-C_2Alkyl, C_1-C_2Alkoxy, Trifluoromethyl, Difluoromethoxy und Trifluoromethoxy ausgewählt sind;
n 1, 2 oder 3 ist, und

unsubstituiert oder mit einem C_1-C_4Alkyl substituenten oder einem Trifluoromethyl substituenten substituiert ist; und
R_2 Phenyl, Naphthyl, Benzo[d][1,3]Dioxolyl, Pyridyl, Thienyl, Furanyl, Indolyl, Imidazolyl, Thiazolyl, Pyrrolidinyl, Piperidinyl, Piperazinyl, Pyrrolyl, Morpholinyl ist, die jeweils unsubstituiert oder mit einem oder mehreren Substituenten substituiert sind, die unabhängig unter Halogen, Hydroxyl, Amino, Cyano, C_1-C_4Alkyl, C_1-C_4Alkoxy, (mono- and di-C_1-C_4Alkylamino)C_0-C_2Alkyl, C_1-C_4Alkylthio, C_1-C_4Alkylsulfonyl, C_1-C_2Haloalkyl und C_1-C_2Haloalkoxy ausgewählt sind;
R_2 Thienyl ist, das unsubstituiert oder mit einem oder mehreren Substituenten substituiert ist, die unabhängig unter Halogen, C_1-C_2Alkyl oder C_1-C_2Alkoxy ausgewählt sind; oder
R_2 Phenyl ist, das unsubstituiert oder mit einem oder mehreren Substituenten substituiert ist, die unabhängig unter Halogen, Hydroxyl, Amino, Cyano, C_1-C_4Alkyl, C_1-C_4Alkoxy, (mono- und di-C_1-C_4Alkylamino)C_0-C_2Alkyl, C_1-C_4Alkylthio, C_1-C_4Alkylsulfonyl, C_1-C_2Haloalkyl und C_1- C_2Haloalkoxy ausgewählt sind.

13. Verbindung oder Salz davon nach Anspruch 1, wobei die Verbindung

10-Ethyl-*N*-(3-Methoxybenzyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-*N*-(2-Methoxybenzyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-Benzyl-10-Ethyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-11-Oxo-*N*-(1-Phenylethyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-*N*-(4-(Methylthio)benzyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-4-tert-Butylbenzyl)-10-Ethyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-*N*-(4-Methylbenzyl)-11-Oxo-10,11,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-11-Oxo-*N*-(4-Trifluoromethyl)benzyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-*N*-(4-(Fluorobenzyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-(4-Cyanobenzyl)-10-Ethyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-N-(4-(Methylsulfonyl)benzyl)-11-Oxo-10,11-Hydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-11-Oxo-N-(3,4,5-Trimethoxybenzyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid

ist;
N-(benzo[d][1,3]Dioxol-5-Ylmethyl)-10-Ethyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-N-(4-Methoxyphenethyl)-11-Oxo-10,11,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-(4-Methoxybenzyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-(4-Methoxybenzyl)-10-Methyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-(4-Methoxybenzyl)-11-Oxo-10-Propyl-10,11-Dihydrodibenzo[b,f][1,4]Thiazepine-8-Carboxamid 5-Oxid ist;
N-Benzyl-10-Methyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-(4-Fluorobenzyl)-10-Methyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-(4-Chlorobenzyl)-10-Methyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-(3-Chlorobenzyl)-10-Methyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-(4-Bromobenzyl)-10-Methyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Methyl-11-Oxo-*N*-(Pyridin-2-ylMethyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Methyl-11-Oxo-N-(Pyridin-3-ylMethyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Methyl-11-Oxo-N-(2-(Thiophen-2-yl)Ethyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Methyl-11-Oxo-N-(2-(Pyrrolidin-1-yl)Ethyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Methyl-11-Oxo-N-(2-(Piperidin-1-yl)Ethyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-(3-(Dimethylamino)propyl)-10-Methyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-N-(4-Methoxybenzyl)-N-Methyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]thiazcpinc-8-Carboxamid 5-Oxid ist;
N-Benzyl-N,10-Diethyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-(4-Methoxybenzyl)Carboxylat 5-Oxid ist;
N-(10-Ethyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-yl)-2-(4-Methoxyphenyl)Acetamid 5-Oxid ist;
N-(10-Ethyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-yl)-2-(4-Fluorophenyl)Acetamid 5-Oxid ist;
10-Ethyl-N-(4-Fluorobenzyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-(S)-Oxid ist;
N-(4-Cyanobenzyl)-10-Ethyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-(S)-Oxid ist;
(R)-N-(1-(4-Bromophenyl)Ethyl)-10-Ethyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-(S)-Oxid ist;
(R)-10-Ethyl-N-(1-(Naphthalen-2-yl)Ethyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-(S)-Oxid ist;
N-(4-Chlorobenzyl)-10-Methyl-11-Oxo-10,11-Dihydrodibenzo[b,f)[1,4]Thiazepin-8-Carboxamid 5-(S)-Oxid ist;
N-(4-Bromobenzyl)-10-Methyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-(S)-Oxid ist;
10-Methyl-11-Oxo-N-(Pyridin-3-ylMethyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-(S)-Oxid ist;
10-Methyl-11-Oxo-N-(2-(Pyrrolidin-1-yl)Ethyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-(S)-Oxid ist;
10-Ethyl-11-Oxo-N-(2-(Thiophen-2-yl)Ethyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Methyl-11-Oxo-N-(2-(Thiophen-2-yl)Ethyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-(S)-Oxid ist;
N-(4-Methoxybenzyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamidist;
10-Ethyl-11-Oxo-N-(3-(Trifluoromethyl)Benzyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-N-(3-Methylbenzyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-(3-Chlorobenzyl)-10-Ethyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-(Biphenyl-3-ylMethyl)-10-Ethyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-11-Oxo-N-(3-Phenylpropyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-(2,3-Dimethoxybenzyl)-10-Ethyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-11-Oxo-N-(Thiophen-2-ylmethyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-N-(Furan-2-ylMethyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-N-((4-Methylthiophen-2-yl)Methyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-N-(2-Morpholinoethyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;

10-Ethyl-N-((1-Methylpiperidin-4-yl)Methyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-(2-Chlorobenzyl)-10-Ethyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-11-Oxo-N-(2-(Trifluoromethyl)benzyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-N-(2-Methylbenzyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-(2,5-Dimethoxybenzyl)-10-Ethyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-((1H-Indol-6-yl)Methyl)-10-Ethyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-(2,4-Dimethoxybenzyl)-10-Ethyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-(4-Cyanobenzyl)-10-Ethyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-(R)-Oxid ist;
N-(2,6-Dimethoxybenzyl)-10-Ethyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-N-(4-Fluorobenzyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-(R)-Oxid ist;
10-Ethyl-N-(4-Methylphenethyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-11-Oxo-N-(4-Phenylbutyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-N-(2-(Furan-2-yl)Propyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-((1H-Imidazol-2-yl)Methyl)-10-Ethyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-N-(2-(2-Methylthiazol-4-yl)Ethyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-N-(3-Methoxyphenethyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-N-((1-Methyl-1H-Imidazol-5-yl)Methyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-N-((2-Methylthiazol-4-yl)Methyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-N-((1-Methyl-1H-Imidazol-4-yl)Methyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-N-(3-Fluorobenzyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-(3-(Dimethylamino)propyl)-10-Ethyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-(4-Aminophenethyl)-10-Ethyl-11-Oxo-10,11-Dihydrodibenzo[b,f)[1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-(4-Methoxybenzyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5,5-DiOxid ist;
N-(4-Chlorobenzyl)-10-Methyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-(R)-Oxid ist;
N-(4-Bromobenzyl)-10-Methyl-11-Oxo-10,11-dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-(R)-Oxid ist;
N-(4-Iodobenzyl)-10-Methyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-(3-Fluorobenzyl)-10-Methyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Methyl-11-Oxo-N-(2-(Thiophen-2-yl)Ethyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-(R)-Oxid ist;
(S)-10-Methyl-11-Oxo-N-(1-Phenylethyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
N-(3,5-Difluorobenzyl)-10-Methyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Methyl-11-oxo-N-(Pyridin-3-ylMethyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-(R)-Oxid ist;
N-(4-(Dimethylamino)butyl)-10-Methyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
(R) -10-Methyl-11-Oxo-N-(1-Phenylethyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
(S) -N-(1-(4-Chlorophenyl)ethyl)-10-Methyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
(R)-N-(1-(4-Chlorophenyl)ethyl)-10-Methyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Methyl-11-Oxo-N-(3-(Piperidin-1-yl)propyl)-10,11-Dihydrodibenzo[b,1][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Methyl-11-Oxo-N-(2,2,2-Trifluoro-1-phenylethyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Ethyl-11-Oxo-N-(2,2,2-Trifluoro-1-Phenylethyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
10-Methyl-11-Oxo-N-(2-(Pyrrolidin-1-yl)ethyl)-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-(R)-Oxid ist;
N-(3,4-Dichlorobenzyl)-10-Methyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
(R)-N-(1-(4-Bromophenyl)ethyl)-10-ethyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-

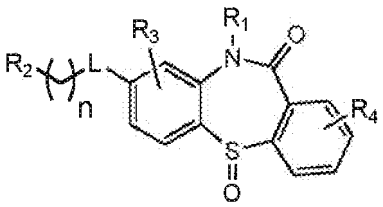
Oxid ist;
(R)-N-(l-(4-Bromophenyl)ethyl)-10-Ethyl-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-(R)-Oxid ist;
(R)-10-Ethyl-N-(1-(Naphthalen-2-yl)Ethyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-Oxid ist;
(R)-10-Ethyl-N-(1-(Naphthalen-2-yl)Ethyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5-(R)-Oxid ist; oder
10-Ethyl-N-(4-Methoxybenzyl)-11-Oxo-10,11-Dihydrodibenzo[b,f][1,4]Thiazepin-8-Carboxamid 5,5-Dioxid.

14. Pharmazeutische Zusammensetzung, die eine Verbindung oder ein Salz nach einem beliebigen der vorstehenden Ansprüche 1 bis 13 und einen pharmazeutisch zulässigen Träger enthält.

15. Verbindung oder Salz nach einem beliebigen der vorstehenden Ansprüche 1 bis 13 zur Verwendung bei der Behandlung von Tourette-Syndrom, bipolarer Störung, Hyperprolaktinämie, Psychose, Depression, Huntington-Chorea oder Schizophrenie.

Revendications

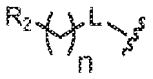
1. Composé de formule :



ou un sel pharmaceutiquement acceptable de celui-ci, où L est -NHC(O)-,-C(O)NH-, -OC(O)- ou -C(O)O- ;

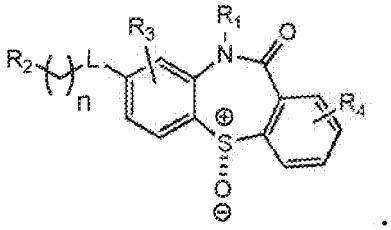
n est un nombre entier de 1 à 4 et

est non substitué ou substitué par un ou plusieurs substituants indépendamment choisis parmi un halogène, hydroxyle, amino, cyano, alkyle C_1-C_4, alcoxy C_1-C_4, halogénoalkyle C_1-C_2, ou halogénoalcoxy C_1-C_2 ;
R_1 est hydrogène, alkyle C_1-C_6, alcényle C_2-C_6, (cycloalkyl(C_3-C_7))alkyle C_0-C_2, (mono- ou dialkyl(C_1-C_4)amino)-alkyle C_1-C_4, ou (mono- ou dialkyl(C_1-C_4)amino)alcoxy C_1-C_4 ;
R_2 est un groupe carbocyclique ou hétérocyclique mono-, bi- ou tricyclique, un groupe (mono- ou dialkyl(C_1-C_4)amino)-alkyle C_2-C_4, ou alkyle C_4-C_8, chacun des R_2 est non substitué ou substitué par un ou plusieurs substituants indépendamment choisis parmi un halogène, hydroxyle, amino, nitro, cyano, alkyle C_1-C_6, alcényle C_2-C_6, alcynyle C_2-C_6, $-OR_{11}$, $-(CH_2)_{0-4}C(O)R_{11}$, $-(CH_2)_{0-4}NR_{11}R_{12}$, $-(CH_2)_{0-4}C(O)NR_{11}R_{12}$, $-(CH_2)_{0-4}N(R_{11})C(O)(R_{12})$, $-(CH_2)_{0-4}C(O)OR_{11}$, $-(CH_2)_{0-4}OC(O)R_{11}$, $-(CH_2)_{0-4}C(S)R_{11}$, $-(CH_2)_{0-4}S(O)_aR_{11}$, $-(CH_2)_{0-4}S(O)_bNR_{11}R_{12}$, $-(CH_2)_{0-4}N(R_{11})S(O)_bR_{12}$, et (phényl) alkyle C_0-C_2, où a est 0, 1, ou 2, et b est 1 ou 2, R_{11}, R_{12} et R_{13} sont indépendamment choisis à chaque occurrence parmi un hydrogène et un groupe aliphatique C_1-C_6 ;
chacun des R_{11}, R_{12} et R_{13} est non substitué ou substitué par un ou plusieurs substituants indépendamment choisis parmi : halogène, hydroxyle, vinyle, allényle, oxo, cyano, amino, -COOH, alkyle C_1-C_6, alcoxy C_1-C_6, (mono- et dialkyl(C_1-C_6)amino)alkyle C_0-C_2, alkyl (C_1-C_6)ester, alkyl (C_1-C_6)thio, halogénoalkyle C_1-C_2 et halogénoalcoxy C_1-C_2 ;
R_3 et R_4 représentent 0 ou 1 substituant ou plus indépendamment choisi parmi un halogène, hydroxyle, amino, cyano, alkyle C_1-C_4, alcoxy C_1-C_4, alcanoyle C_2-C_4, (mono- et dialkyl (C_1-C_4)amino)alkyle C_0-C_2, halogénoalkyle C_1-C_2 et halogénoalcoxy C_1-C_2 ;
à condition que quand R_1 est éthyle, le groupe

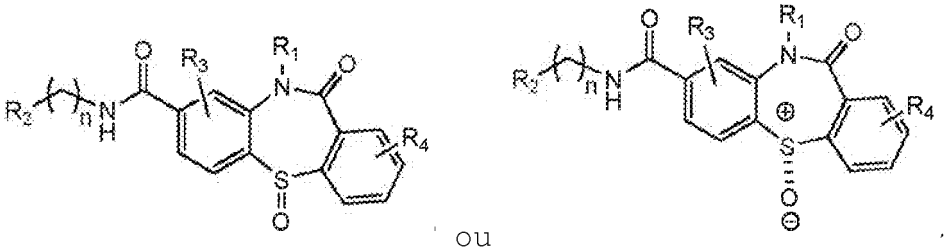


ne soit pas 4-méthoxybenzyl-NHC(O)-, pyridin-2-ylméthyl-NHC(O)-, 3-(morpholin-1-yl)propyl-NHC(O)-, 3-(azépan-1-yl)-propyl-NHC(O)-, 3-(azépan-1-yl)éthyl-NHC(O)-, 3-(pyrrolidin-1-yl)propyl-NHC(O)-, 3-(4-méthylpipérazin-1-yl)-propyl-NHC(O)-, 3-(pipéridin-1-yl)propyl-NHC(O)-, di-isopropylaminopropyl-NHC(O)-, di-propylaminopropyl-NHC(O)-, di-butylaminopropyl-NHC(O)-, ou 3-(butyl)(éthyl)amino)propyl- NHC(O)-.

2. Composé ou sel selon la revendication 1, de formule



3. Composé ou sel selon la revendication 1, de formule



ou

4. Composé ou sel selon l'une quelconque des revendications 1 à 3, où
R_1 est alkyle C_1-C_6, alcényle C_2-C_6, ou (cycloalkyl-(C_3-C_7))alkyle C_0-C_2, de préférence alkyle C_1-C_6.

5. Composé ou sel selon l'une quelconque des revendications 1 à 4, où
R_1 est méthyle ou éthyle, et R_3 et R_4 représentent tous deux 0 substituant.

6. Composé ou sel selon l'une quelconque des revendications 1 à 4, où
R_3 et R_4 représentent tous deux 0, 1, ou 2 substituants indépendamment choisis parmi un halogène, hydroxyle, amino, cyano, alkyle C_1-C_2, alcoxy C_1-C_2, trifluorométhyle, difluorométhoxy, et trifluorométhoxy.

7. Composé ou sel selon l'une quelconque des revendications 1 à 6, où n est 1, 2, ou 3 et

est non substitué ou substitué par un substituant alkyle C_1-C_4 ou un substituant trifluorométhyle.

8. Composé ou sel selon la revendication 7, où n est 1 ou 2 et

est non substitué ou substitué par un substituant méthyle.

9. Composé ou sel selon l'une quelconque des revendications 1 à 8, où

R_2 est un cycloalkyle C_3-C_7, hétérocycloalkyle de 5 ou 6 chaînons contenant 1 ou 2 hétéroatomes choisis parmi N, 0, ou S, phényle, naphtyle, phényle fusionné à un cycle hétérocyclique de 5 ou 6 chaînons contenant 1 ou 2 atomes d'oxygène, pyridyle, pyrimidinyle, pyrazinyle, thiényle, furanyle, pyrrolyle, thiazolyle, indolyle, ou imidazolyle, chacun des R_2 est non substitué ou substitué par un ou plusieurs substituants indépendamment choisis parmi un halogène, hydroxyle, amino, cyano, alkyle C_1-C_4, alcoxy C_1-C_4, (mono- et dialkyl- (C_1-C_4)amino) alkyle C_0-C_2, alkyl (C_1-C_4)thio, alkyl (C_1-C_4)-sulfonyle, halogénoalkyle C_1-C_2, et halogénoalcoxy C_1-C_2 .

10. Composé ou sel selon la revendication 9, où
R_2 est phényle, napthyle, benzo[d][1,3]dioxolyle, pyridyle, thiényle, furanyle, indolyle, imidazolyle, thiazolyle, pyrrolidinyle, pipéridinyle, pipérazinyle, pyrrolyle, morpholinyle, chacun substitué par un ou plusieurs substituants indépendamment choisis parmi un halogène, hydroxyle, amino, cyano, alkyle C_1-C_4, alcoxy C_1-C_4, (mono- et dialkyl (C_1-C_4)amino)alkyle C_0-C_2, alkyl (C_1-C_4)thio, alkyl (C_1-C_4)sulfonyle, halogénoalkyle C_1-C_2 et halogénoalcoxy C_1-C_2.

11. Composé ou sel selon la revendication 9, où
R_2 est phényle, napthyle, benzo[d][1,3]dioxolyle, pyridyle, thiényle, pyrrolidinyle, pipéridinyle, pipérazinyle, chacun substitué par un ou plusieurs substituants indépendamment choisis parmi un halogène, hydroxyle, cyano, alkyle C_1-C_4, alcoxy C_1-C_4, méthylthio, méthylsulfonyle, trifluorométhyle et trifluorométhoxy.

12. Composé ou sel selon la revendication 3, où
R_1 est alkyle C_1-C_6 ou (cycloalkyl(C_3-C_7))alkyle C_0-C_2 ;
R_3 et R_4 représentent tous deux 0, 1, ou 2 substituants indépendamment choisis parmi un halogène, hydroxyle, amino, cyano, alkyle C_1-C_2, alcoxy C_1-C_2, trifluorométhyle, difluorométhoxy, et trifluorométhoxy ;
n est 1, 2 ou 3 et

est non substitué ou substitué par un substituant alkyle C_1-C_4 ou un substituant trifluorométhyle ; et
R_2 est phényle, napthyle, benzo[d][1,3]dioxolyle, pyridyle, thiényle, furanyle, indolyle, imidazolyle, thiazolyle, pyrrolidinyle, pipéridinyle, pipérazinyle, pyrrolyle, morpholinyle, chacun non substitué ou substitué par un ou plusieurs substituants indépendamment choisis parmi un halogène, hydroxyle, amino, cyano, alkyle C_1-C_4, alcoxy C_1-C_4, (mono- et dialkyl (C_1-C_4)amino) alkyle C_0-C_2, alkyl (C_1-C_4)thio, alkyl(C_1-C_4)sulfonyle, halogénoalkyle C_1-C_2 et halogénoalcoxy C_1-C_2 ;
R_2 est thiényle, qui est non substitué ou substitué par un ou plusieurs substituants indépendamment choisis parmi un halogène, alkyle C_1-C_2, ou alcoxy C_1-C_2 ; ou
R_2 est un phényle qui est non substitué ou substitué par un ou plusieurs substituants indépendamment choisis parmi un halogène, hydroxyle, amino, cyano, alkyle C_1-C_4, alcoxy C_1-C_4, (mono- et dialkyl (C_1-C_4)amino) alkyle C_0-C_2, alkyl (C_1-C_4)thio, alkyl(C_1-C_4)sulfonyle, halogénoalkyle C_1-C_2 et halogénoalcoxy C_1-C_2 .

13. Composé ou sel de celui-ci selon la revendication 1, dans lequel le composé est un

5-oxyde de 10-éthyl-*N*-(3-méthoxybenzyl)-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-*N*-(2-méthoxybenzyl)-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de *N*-benzyl-10-éthyl-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-11-oxo-*N*-(1-phényléthyl)-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-*N*-(4-(méthylthio)benzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de *N*-(4-tert-butylbenzyl)-10-éthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-N-(4-méthylbenzyl)-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-11-oxo-*N*-(4-(trifluorométhyl)benzyl)-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-N-(4-fluorobenzyl)-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-(4-cyanobenzyl)-10-éthyl-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-N-(4-(méthylsulfonyl)benzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-11-oxo-N-(3,4,5-triméthoxybenzyl)-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;

5-oxyde de N-(benzo[d][1,3]dioxol-5-ylméthyl)-10-éthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-N-(4-méthoxyphénéthyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-(4-méthoxybenzyl)-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-(4-méthoxybenzyl)-10-méthyl-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-(4-méthoxybenzyl)-11-oxo-10-propyl-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-benzyl-10-méthyl-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-(4-fluorobenzyl)-10-méthyl-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-(4-chlorobenzyl)-10-méthyl-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-(3-chlorobenzyl)-10-méthyl-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-(4-bromobenzyl)-10-méthyl-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-méthyl-11-oxo-N-(pyridin-2-ylméthyl)-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-méthyl-11-oxo-N-(pyridin-3-ylméthyl)-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-méthyl-11-oxo-N-(2-(thiophén-2-yl)éthyl)-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-méthyl-11-oxo-N-(2-(pyrrolidin-1-yl)éthyl)-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-méthyl-11-oxo-N-(2-(pipéridin-1-yl)éthyl)-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-(3-(diméthylamino)propyl)-10-méthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-N-(4-méthoxybenzyl)-N-méthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-benzyl-N,10-diéthyl-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4] thiazépine-8-(4-méthoxybenzyl)carboxylate ;
5-oxyde de N-(10-éthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4] thiazépin-8-yl)-2-(4-méthoxyphényl)acétamide ;
5-oxyde de N-(10-éthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4] thiazépin-8-yl)-2-(4-fluorophényl)acétamide ;
5-(S)-oxyde de 10-éthyl-N-(4-fluorobenzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4] thiazépine-8-carboxamide ;
5-(S)-oxyde de N-(4-cyanobenzyl)-10-éthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4] thiazépine-8-carboxamide ;
5-(S)-oxyde de (R)-N-(1-(4-bromophényl)éthyl)-10-éthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4] thiazépine-8-carboxamide ;
5-(S)-oxyde de (R)-10-éthyl-N-(1-(naphtalén-2-yl)éthyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-(S)-oxyde de N-(4-chlorobenzyl)-10-méthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-(S)-oxyde de N-(4-bromobenzyl)-10-méthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-(S)-oxyde de 10-méthyl-11-oxo-N-(pyridin-3-ylméthyl)-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-(S)-oxyde de 10-méthyl-11-oxo-N-(2-(pyrrolidin-1-yl)éthyl)-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-11-oxo-N-(2-(thiophén-2-yl)éthyl)-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-(S)-oxyde de 10-méthyl-11-oxo-N-(2-(thiophén-2-yl)éthyl)-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
N-(4-méthoxybenzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]-thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-11-oxo-N-(3-(trifluorométhyl)benzyl)-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-N-(3-méthylbenzyl)-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-(3-chlorobenzyl)-10-éthyl-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-(biphényl-3-ylméthyl)-10-éthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-11-oxo-N-(3-phénylpropyl)-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-(2,3-diméthoxybenzyl)-10-éthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-11-oxo-N-(thiophén-2-ylméthyl)-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;

5-oxyde de 10-éthyl-N-(furan-2-ylméthyl)-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-N-((4-méthylthiophén-2-yl)méthyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-N-(2-morpholinoéthyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-N-((1-méthylpipéridin-4-yl)méthyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-(2-chlorobenzyl)-10-éthyl-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-11-oxo-N-(2-(trifluorométhyl)benzyl)-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-N-(2-méthylbenzyl)-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-(2,5-diméthoxybenzyl)-10-éthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-((lH-indol-6-yl)méthyl)-10-éthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-(2,4-diméthoxybenzyl)-10-éthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-(R)-oxyde de N-(4-cyanobenzyl)-10-éthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-(2,6-diméthoxybenzyl)-10-éthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-(R)-oxyde de 10-éthyl-N-(4-fluorobenzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-N-(4-méthylphénéthyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-11-oxo-N-(4-phénylbutyl)-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-N-(2-(furan-2-yl)propyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-((1H-imidazol-2-yl)méthyl)-10-éthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-N-(2-(2-méthylthiazol-4-yl)éthyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-N-(3-méthoxyphénétyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-N-((1-méthyl-1H-imidazol-5-yl)méthyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-N-((2-méthylthiazol-4-yl)méthyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-N-((1-méthyl-1H-imidazol-4-yl)méthyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-N-(3-fluorobenzyl)-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-(3-(diméthylamino)propyl)-10-éthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-(4-aminophénéthyl)-10-éthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5,5-dioxyde de N-(4-méthoxybenzyl)-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-(R)-oxyde de N-(4-chlorobenzyl)-10-méthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-(R)-oxyde de N-(4-bromobenzyl)-10-méthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-(4-iodobenzyl)-10-méthyl-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-(3-fluorobenzyl)-10-méthyl-11-oxo-10,11-dihydro-dibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-(R)-oxyde de 10-méthyl-11-oxo-N-(2-(thiophén-2-yl)éthyl)-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de (S)-10-méthyl-11-oxo-N-(1-phényléthyl)-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-(3,5-difluorobenzyl)-10-méthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-(R)-oxyde de 10-méthyl-11-oxo-N-(pyridin-3-ylméthyl)-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-(4-(diméthylamino)butyl)-10-méthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de (R)-10-méthyl-11-oxo-N-(1-phényléthyl)-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de (S)-N-(1-(4-chlorophényl)éthyl)-10-méthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de (R)-N-(1-(4-chlorophényl)éthyl)-10-méthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-car-

boxamide ;
5-oxyde de 10-méthyl-11-oxo-N-(3-(pipéridin-1-yl)propyl)-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-méthyl-11-oxo-N-(2,2,2-trifluoro-1-phényléthyl)-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de 10-éthyl-11-oxo-N-(2,2,2-trifluoro-1-phényléthyl)-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-(R)-oxyde de 10-méthyl-11-oxo-N-(2-(pyrrolidin-1-yl)éthyl)-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de N-(3,4-dichlorobenzyl)-10-méthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de (R)-N-(1-(4-bromophényl)éthyl)-10-éthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-(R)-oxyde de (R)-N-(1-(4-bromophényl)éthyl)-10-éthyl-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-oxyde de (R)-10-éthyl-N-(1-(naphtalén-2-yl)éthyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ;
5-(R)-oxyde de (R)-10-éthyl-N-(1-(naphtalén-2-yl)éthyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide ; ou
5,5-dioxyde de 10-éthyl-N-(4-méthoxybenzyl)-11-oxo-10,11-dihydrodibenzo[b,f][1,4]thiazépine-8-carboxamide.

14. Composition pharmaceutique comprenant un composé ou un sel selon l'une quelconque des revendications 1 à 13 et un véhicule pharmaceutiquement acceptable.

15. Composé ou sel selon l'une quelconque des revendications 1 à 13, pour une utilisation dans le traitement du syndrome de Tourette, du trouble bipolaire, de l'hyperprolactinémie, de la psychose, de la dépression, de la maladie de Huntington, ou de la schizophrénie.

FIG. 1A

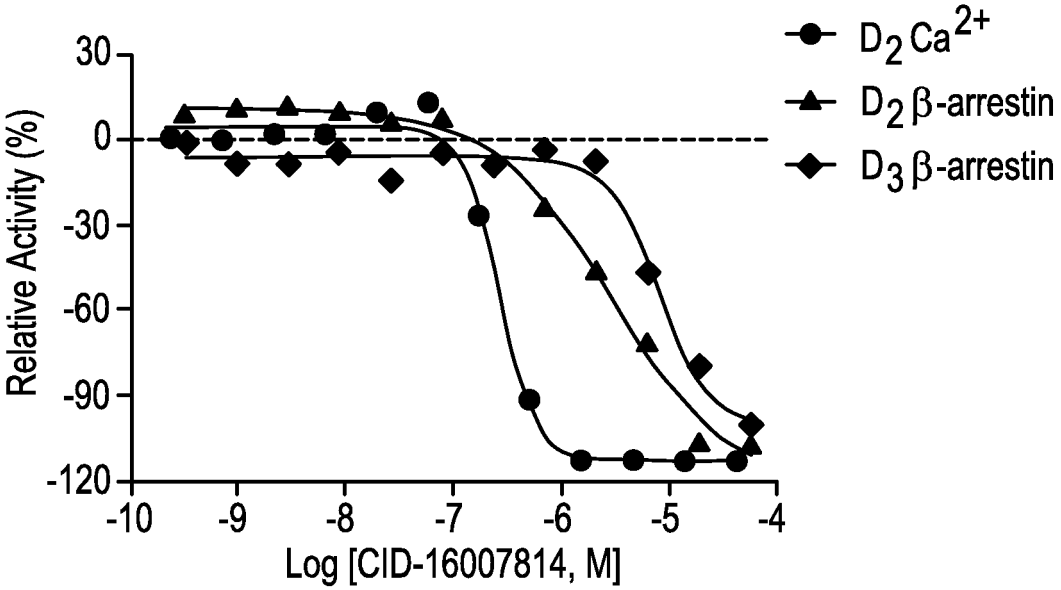

30
0
-30
-60
-90
-120
Relative Activity (%)
-10
-9
-8
-7
-6
-5
-4
Log [CID-16007814, M]
D2 Ca2+
D2 β-arrestin
D3 β-arrestin

FIG. 1B

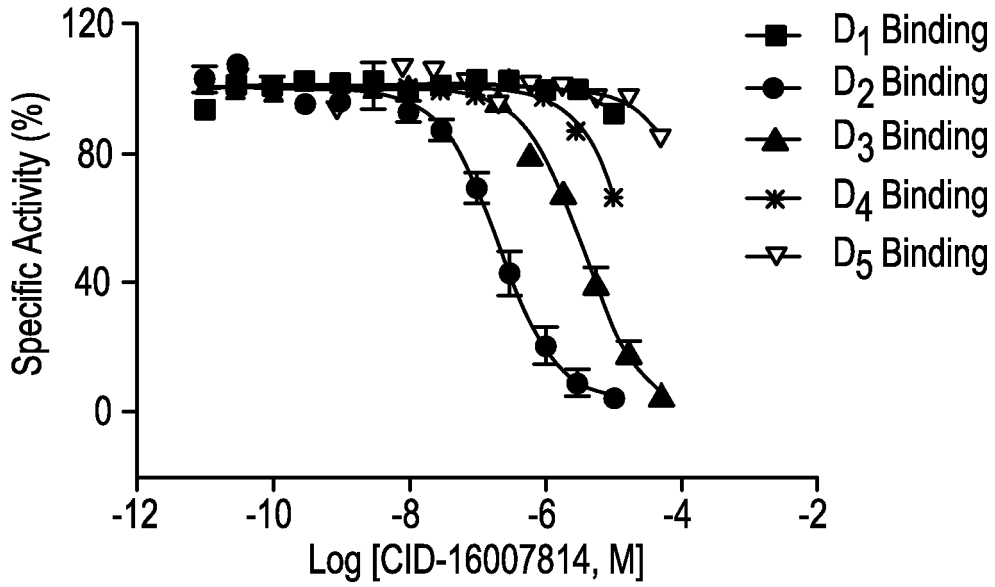

120
80
40
0
Specific Activity (%)
-12
-10
-8
-6
-4
-2
Log [CID-16007814, M]
D1 Binding
D2 Binding
D3 Binding
D4 Binding
D5 Binding

FIG. 2A

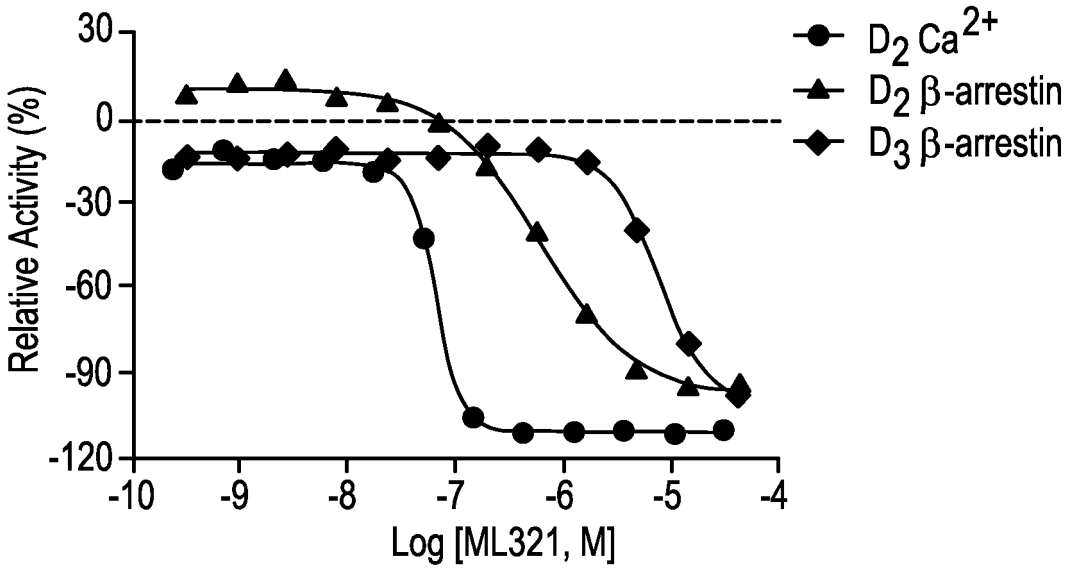
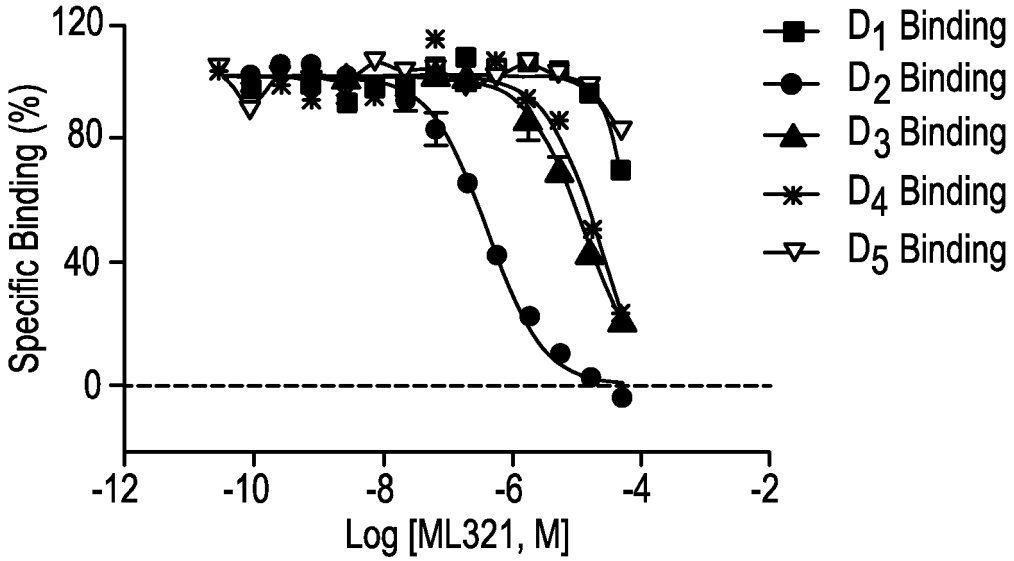

30
0
-30
-60
-90
-120
Relative Activity (%)
-10
-9
-8
-7
-6
-5
-4
Log [ML321, M]
D2 Ca2+
D2 β-arrestin
D3 β-arrestin

FIG. 2B


120
80
40
0
Specific Binding (%)
-12
-10
-8
-6
-4
-2
Log [ML321, M]
D1 Binding
D2 Binding
D3 Binding
D4 Binding
D5 Binding

REFERENCES CITED IN THE DESCRIPTION

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Non-patent literature cited in the description

- Remington's Pharmaceutical Sciences. Mack Publishing Company, 1985, 1418 **[0045]**
- **COLLINS et al.** *Psychopharmacology (Berl),* 2007, vol. 193 (2), 159-70 **[0368]**